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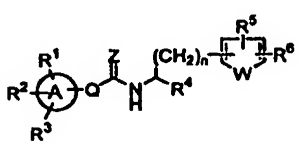

(I)

(57) Abstract

The present invention relates to a pharmaceutical composition comprising as an active ingredient a compound of formula (I), wherein Ring A is an aromatic or a heterocyclic ring; Q is a bond, carbonyl, lower alkylene, lower alkenylene, -O-(lower alkylene)-, etc.; n is 0, 1 or 2; Z is oxygen or sulfur; W is oxygen, sulfur, -CH=CH-, -NH- or -N=CH-; R^1, R^2 and R^3 are the same or different and are hydrogen, halogen, hydroxyl, a substituted or unsubstituted lower alkyl group, a substituted or unsubstituted lower alkoxy group, a substituted or unsubstituted amino group, etc.; R^4 is tetrazolyl, carboxyl group, amide or ester; R^5 is hydrogen, nitro, amino, hydroxyl, lower alkanoyl, lower alkyl, etc.; R^6 is selected from (a) a substituted or unsubstituted phenyl group, (b) a substituted or unsubstituted pyridyl group, (c) a substituted or unsubstituted thienyl group, (d) a substituted or unsubstituted benzofuranyl group, etc.; or a pharmaceutically acceptable salt thereof.

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INHIBITORS OF $\alpha 4$ MEDIATED CELL ADHESION

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates to pharmaceutical compositions comprising molecules that are inhibitors of $\alpha 4$ mediated (including $\alpha_4\beta_7$) adhesion and which could be useful in treating conditions such as asthma, diabetes, rheumatoid arthritis, inflammatory bowel disease and other diseases involving leukocyte infiltration of the gastrointestinal tract or other epithelial lined tissues; such as, skin, urinary tract, respiratory airway and joint synovium.

The inhibitors of the present invention could also be useful in treating conditions involving leukocyte infiltration of other tissues including lung, blood vessels, heart and nervous system as well as transplanted organs such as kidney, liver, pancreas and heart.

Description of the Related Art

The adhesion of leukocyte to endothelial cells or extracellular matrix proteins is a fundamental process for immunity and inflammation and involves multiple adhesive interactions. The earliest events in this process include leukocyte rolling followed by changes in integrin avidity, which leads to subsequent firm adhesion (for reviews see Butcher, *Cell* 67:1033-1036 (1991); Harlan, *Blood* 3:513-525 (1985); Hemler, *Annu. Rev. Immunol.* 8:365-400 (1990);

Osborn, *Cell* 62:3-6 (1990); Shimizu et al., *Immunol. Rev.* 114:109-143 (1990); Springer, *Nature* 346:425-434 (1990); Springer, *Cell* 76:301-314 (1994)). In response to chemotactic factors, the leukocytes must migrate through two adjacent endothelial cells and into tissues that are composed, in part, of the extracellular matrix protein fibronectin (FN) (see Wayner et al., *J. Cell Biol.* 105:1873-1884 (1987)) and collagen (CN) (see Bornstein et al., *Ann. Rev. Biochem.* 49:957-1003 (1980) and Miller, Chemistry of the collagens and their distribution. In Connective Tissue Biochemistry. K.A. Piez and A.H. Reddi, editors. Elsevier, Amsterdam. 41-78. (1983)) Important recognition molecules that participate in these reactions belong to the integrin gene superfamily (for reviews see Hemler, *Annu. Rev. Immunol.* 8:365-400 (1990); Hynes, *Cell* 48:549-554 (1987); Shimizu et al., *Immunol. Rev.* 114:109-143 (1990); and Springer, *Nature* 346:425-434 (1990)).

Integrins are composed of non-covalently associated subunits, referred to as the alpha (α) and beta (β) subunits (for reviews see Hemler, *Annu. Rev. Immunol.* 8:365-400 (1990); Hynes, *Cell* 48:549-554 (1987); Shimizu et al., *Immunol. Rev.* 114:109-143 (1990); and Springer, *Nature* 346:425-434 (1990)). To date, 8 integrin β subunits have been identified which can associate with 16 distinct α subunits to form 22 distinct integrins. The $\beta 7$ integrin subunit, first cloned by Erle et al., (Erle et al., *J. Biol. Chem.* 266:11009-11016 (1991)) is expressed only on leukocytes and is known to associate with two distinct α subunits, $\alpha 4$ (Ruegg et al., *J. Cell Biol.* 117:179-189 (1992)) and αE (Cerf-Bensussan et al., *Eur. J. Immunol.* 22:273-277 (1992) and Kilshaw et al., *Eur. J. Immunol.* 21:2591-2597 (1991)). The $\alpha E\beta 7$ heterodimer has E-cadherin as its sole ligand.

The $\alpha4\beta7$ complex has three known ligands (VCAM, CS-1, MAdCAM). One ligand which shows unique specificity for $\alpha4\beta7$ is Mucosal Addressing Cell Adhesion Molecule (MAdCAM) (see Andrew et al., *J. Immunol* 153:3847-3861 (1994); Briskin et al., *Nature* 363:461-464 (1993); and Shyjan et al., *J. Immunol* 156:2851-2857 (1996)). MAdCAM is highly expressed on Peyer's patch high endothelial venules, in mesenteric lymph nodes, and on gut lamina propria and mammary gland venules (Berg et al., *Immunol. Rev.* 105:5 (1989)). Integrin $\alpha4\beta7$ and MAdCAM have been shown to be important in regulating lymphocyte trafficking to normal intestine (Holzmann et al., *Cell* 56:37 (1989)).

The second ligand for $\alpha4\beta7$ is connecting segment 1 (CS-1), an alternatively spliced region of the FN A chain (see Guan et al., *Cell* 60:53-61 (1990) and Wayner et al., *J. Cell Biol.* 109:1321-1330 (1989)). The cell-binding site within this alternatively spliced region is composed of 25 amino acids where the carboxy terminal amino acid residues, EILDVPST, form the recognition motif (see Komoriya et al., *J. Biol. Chem.* 266:15075-15079 (1991) and Wayner et al., *J. Cell Biol.* 116:489-497 (1992)).

The third ligand for $\alpha4\beta7$ is vascular cell adhesion molecule 1 (VCAM-1), a cytokine inducible protein expressed on endothelial cells (see Elices et al., *Cell* 60:577-584 (1990) and Ruegg et al., *J. Cell Biol.* 117:179-189 (1992)). VCAM and CS-1 (see Elices et al., *Cell* 60:577-584 (1990)) are two ligands which are shared by $\alpha4\beta7$ and $\alpha4\beta1$. It remains to be unequivocally shown whether MAdCAM, VCAM and CS-1 bind to the same site on $\alpha4\beta7$. Using a panel of monoclonal antibodies, Andrew et al., showed that $\alpha4\beta7$ interaction with its three ligands involve distinct but overlapping epitopes (Andrew et al., *J. Immunol* 153:3847-3861 (1994)).

Utility of the Invention

A number of *in vitro* and *in vivo* studies indicate that α4 plays a critical role in the pathogenesis of a variety of diseases. Monoclonal antibodies directed against α4 have been tested in a variety of disease models. Efficacy of anti-α4 antibody was demonstrated in a rat and mouse model of experimental autoimmune encephalomyelitis (see Baron et al., *J. Exp. Med.* 177:57-68 (1993) and Yednock et al., *Nature* 356:63-66 (1992)). A significant number of studies have been done to evaluate the role of α4 in allergic airways (see Abraham et al., *J. Clin. Invest.* 93:776-787 (1994); Bochner et al., *J. Exp. Med.* 173:1553-1556 (1991); Walsh et al., *J. Immunol* 146:3419-3423 (1991); and Weg et al., *J. Exp. Med.* 177:561-566 (1993)). For example, monoclonal antibodies to α4 were effective in several lung antigen challenge models (see Abraham et al., *J. Clin. Invest.* 93:776-787 (1994) and Weg et al., *J. Exp. Med.* 177:561-566 (1993)). Interestingly, blockade of cellular recruitment is not seen in certain lung models even though there is abrogation of the late phase response (see Abraham et al., *J. Clin. Invest.* 93:776-787 (1994)). The cotton-top tamarin, which experiences spontaneous chronic colitis, showed a significant attenuation of colitis when anti-α4 antibody was administered (see Bell et al., *J. Immunol.* 151:4790-4802 (1993) and Podolsky et al., *J. Clin. Invest.* 92:372-380 (1993)). Monoclonal antibody to α4 inhibits insulitis and delays the onset of diabetes in the non-obese diabetic mouse (see Baron et al., *J. Clin. Invest.* 93:1700-1708 (1994); Burkly et al., *Diabetes* 43:529-534 (1994); and Yang et al., *Proc. Natl. Acad. Sci. USA* 90:10494-10498 (1993)). Other diseases where α4 has been implicated include rheumatoid arthritis (see Laffon et

al., *J. Clin. Invest.* 88:546-552 (1991) and Morales-Ducret et al., *J. Immunol.* 149:1424-1431 (1992)) and atherosclerosis (see Cybulsky et al., *Science* 251:788-791 (1991)). Delayed type hypersensitivity reaction (see Issekutz, *J. Immunol.* 147:4178-4184 (1991)) and contact hypersensitivity response (see Chisholm et al., *Eur. J. Immunol.* 23:682-688 (1993) and Ferguson et al., *J. Immunol.* 150:1172-1182 (1993)) are also blocked by anti-α4 antibodies. For an excellent review of *in vivo* studies implicating α4 in disease (see Lobb et al., *J. Clin. Invest.* 94:1722-1728 (1995)).

Although these studies clearly implicate α4 in a variety of diseases, it is not clear whether the inhibition seen was due to blocking α4β1, α4β7, or both. Recently, several studies have addressed this issue using an antibody which recognizes the α4β7 complex (see Hesterberg et al., *Gastroenterology* (1997)), antibodies against β7 or antibodies directed against MAdCAM (see Picarella et al., *J. Immunol.* 158:2099-2106 (1997)), for which α4β1 does not bind. In the primate model of inflammatory bowel disease, it was shown that antibodies to the α4β7 complex ameliorated inflammation and decreased diarrhea (see Hesterberg et al., Gastroenterology, 111:1373-1380 (1996)). In a second model, monoclonal antibodies to β7 or MAdCAM blocked recruitment of lymphocytes to the colon and reduced the severity of inflammation in the colon of scid mice reconstituted with $CD45RB^{high}$ $CD4^{+}$ cells (see Picarella et al., *J. Immunol.* 158:2099-2106 (1997)). This, together with the fact that gut-associated lymphoid tissue is severely impaired in β7 knock out mice, suggests that α4β7 may be an important intervention point for inflammatory bowel disease.

The expression of $\alpha4\beta7$ on a variety of leukocytes and the increase in $\alpha4\beta7$ positive cells in diseased tissues implicates that the receptor may play an important role in cellular recruitment to other sites of inflammation in addition to trafficking to the gut. $CD4^+$, $CD8^+$ T-cells, B-cells, NK cells, and eosinophils from human peripheral blood were shown to express high levels of $\alpha4\beta7$ (see Picarella et al., *J. Immunol.* 158:2099-2106 (1997)). Increased numbers of $\alpha4\beta7$+ T-cells were found in the synovial membrane of rheumatoid arthritis patients and it was predicted that the augmented expression of $\alpha4\beta7$ may contribute to the development and perpetuation of this disease (see Lazarovits et al., *J. Immunol.* 151:6482-6489 (1993)). In the nonobese diabetic mouse, MAdCAM was expressed on high endothelial venules in inflamed islets within the pancreas suggesting a role for $\alpha4\beta7$ in diabetes (see Kelner et al., *Science* 266:1395-1399 (1994)). The distribution of $\alpha4\beta7$ on lymphocytes and eosinophils (see Erle et al., *J. Immunol.* 153:517-528 (1994)), together with in vitro studies showing that $\alpha4\beta7$ mediates human eosinophil adhesion to VCAM, CS-1 and MAdCAM (see Walsh et al., (Immunology 89:112-119, 1996), suggests that this integrin may be a target molecule in asthma. Collectively, these data suggest that integrin $\alpha4\beta7$ may play an important role in a variety of inflammatory diseases.

N-terminal domain (domain 1) of MAdCAM has homology to the N-terminal integrin recognition domains in both VCAM and ICAM (see Briskin et al., *Nature* 363:461-464 (1993)). Using site-directed mutagenesis on MAdCAM, the binding motif was identified in the first domain as three linear amino acid residues within a C-D loop (see Viney et al., *J. Immunol.* 157:2488-2497 (1996)). Mutations of L40, D41 and T42 resulted in a complete loss of binding activity to

α4β7, suggesting that LDT on MAdCAM is involved in binding loop (see Viney et al., *J. Immunol.* 157:2488-2497 (1996)). Alignment of this region on MAdCAM with other integrin ligands such as VCAM or CS-1 reveals that there is a conserved binding motif or consensus sequence, consisting of G/Q I/L E/D T/S and P/S residues (see Briskin et al., *J. Immunol.* 156:719-726 (1996)). Further support comes from the fact that linear and cyclic peptides containing LDT were shown to block cell adhesion to MAdCAM *in vitro* (see Shroff et al., *Bioorganic & Medicinal Chemistry Letters* 6:2495-2500 (1996) and Viney et al., *J. Immunol.* 157:2488-2497 (1996)).

The use of monoclonal antibodies against integrins *in vivo* has demonstrated that a number of integrins are indeed valid therapeutic targets for inflammatory and cardiovascular diseases and in organ transplantation. The objective here was to define an orally bioavailable, non-peptide, small molecule antagonist of α4β7. Small molecules that are potent inhibitors of α4β7 mediated adhesion to either MAdCAM, VCAM, or CS-1 and which could be useful for the treatment of inflammatory disease are disclosed.

Abbreviations:

BOP-Cl: Bis(2-oxo-3-oxazolidinyl)phosphinic chloride
BOP reagent : Benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate
DCC: 1,3-Dicyclohexylcarbodiimide
EDC: 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
THF: Tetrahydrofuran
DMF: N,N-Dimethylformamide
DIEA: Diisopropylethylamine
DMAP: 4-(N,N-Dimethylamino)pyridine

DBU:	1,8-Diazabicyclo[5.4.0]undec-7-ene
CDI:	Carbonyldiimidazole
HOBT:	1-Hydroxybenzotriazole
Boc:	tert-Butoxycarbonyl
Tf_2O:	Triflic anhydride
Tf:	Trifluoromethanesulfonyl
TFA:	Trifluoroacetic acid
DME:	1,2-Dimethoxyethane
MsCl:	Methanesulfonyl chloride
DIAD:	Diisopropyl azodicarboxylate
Ac:	Acetyl
Me:	Methyl
Et:	Ethyl
Ph:	Phenyl
Bn:	Benzyl
EtOAc:	Ethyl acetate (=AcOEt)
mCPBA:	m-Chloroperbenzoic acid
TMS:	Trimethylsilyl
h:	hour(s)
min:	minute(s)
satd:	Saturated

Additionally, several phrases are utilized for which specific meanings and interpretations exist. These are as follows:

The use of "lower" preceding a group such as alkyl, alkoxy, alkylene or alkane are meant to encompass 1 to 6 carbon atoms either in a straight chain or in a branched chain and the use of "lower" preceding alkanoyl, alkenyl, or alkenylene are meant to encompass 2 to 7 carbon atoms either in a straight chain or in a branched chain. The use of "lower" preceding cycloalkyl or cycloalkoxy are meant to encompass 3 to 7 carbon atoms.

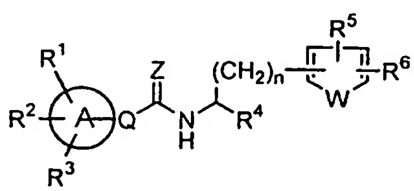
The use of phrases such as "morpholino-lower alkyl", "hydroxy-lower alkoxy" and the like are meant to refer to

groups wherein the functional group preceding the hyphen is a substituent of the functional group that follows the hyphen. For example, "hydroxy-lower alkoxy" would refer to a lower alkoxy group containing at least one hydroxy substituent.

The use of phrases such as "a lower alkyl group substituted by a halogen atom", "phenyl group substituted by a lower alkoxy group" and the like are meant to refer to functional groups containing at least one substituent. For example, "a lower alkyl group substituted by a halogen atom" would refer to a lower alkyl group containing at least one halogen atom, and "phenyl group substituted by a lower alkoxy group" would refer to at least one lower alkoxy group. This type of phraseology is meant to be interpreted by one of skill in the art, therefore, any deviations and combinations of this type of nomenclature is also within the abilities of those skilled in the art to interpret. Accordingly, this type of nomenclature is not to be applied to combinations that would not result in a realistic type of molecule or substituent.

SUMMARY OF THE INVENTION

The present invention relates to a pharmaceutical composition comprising therapeutically effective amount of a compound of the formula [I]:



[I]

wherein

Ring A is an aromatic hydrocarbon ring or a heterocyclic ring;

Q is a bond, a carbonyl group, a lower alkylene group which may be substituted by a hydroxyl group or phenyl group, a lower alkenylene group, or a -O-(lower alkylene)-group;

n is an integer of 0, 1 or 2;

W is oxygen atom, sulfur atom, a -CH=CH- group or a -N=CH- group;

Z is oxygen atom or sulfur atom;

R^1, R^2 and R^3 are the same or different and are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a substituted or unsubstituted lower alkyl group,

d) a substituted or unsubstituted lower alkoxy group,

e) a nitro group,

f) a substituted or unsubstituted amino group,

g) a carboxyl group or an amide or an ester thereof,

h) a cyano group,

i) a lower alkylthio group,

j) a lower alkanesulfonyl group,

k) a substituted or unsubstituted sulfamoyl group,

l) a substituted or unsubstituted aryl group,

m) a substituted or unsubstituted heterocyclic group, and

n) hydroxyl group;

or two of R^1, R^2 and R^3 may combine each other at the terminal thereof to form a lower alkylenedioxy group;

R^4 is tetrazolyl group, a carboxyl group, or an amide or an ester thereof;

R^5 is a group selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) a substituted or unsubstituted amino group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a substituted or unsubstituted lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom, and

i) 2-oxopyrrolidinyl group;

R^6 is a group selected from the group consisting of :

a) a substituted or unsubstituted phenyl group, and

b) a substituted or unsubstituted heteroaryl group;

or a pharmaceutically acceptable salt thereof.

The present invention also relates to a method for treating or preventing conditions caused by α_4 (including $\alpha_4\beta_7$ and $\alpha_4\beta_1$) mediated cell adhesion which comprises administering a compound of the formula [I].

Further, the present invention also relates to a novel compound, which is a compound of the formula [I] with the proviso that when Ring A is a benzene ring, it is not substituted with methyl group in the 3- and the 5-positions or in the 2- and the 4-positions; or a pharmaceutically acceptable salt thereof.

DETAILED DESCRIPTION OF THE INVENTION

The novel compound of the present invention may exist in the form of optical isomers based on asymmetric carbon atoms thereof, and the present invention also includes these optical isomers and mixtures thereof.

In an embodiment of the present invention, the steric configuration of the compound need not be fixed. The compound of the present invention may be a compound with a sole configuration or a mixture thereof with several different configurations.

In the above formula (I), "aromatic hydrocarbon ring" may be a mono-, bi- or tri-cyclic aromatic hydrocarbon ring

such as a benzene ring, a naphthalene ring, an anthracene ring, a fluorene ring.

In the above formula (I), "heterocyclic ring" may be a heteroatom-containing mono-, bi- or tri-cyclic ring. Examples of "heterocyclic ring" may be pyridine ring, pyrimidine ring, pyridazine ring, pyrazine ring, quinoline ring, isoquinoline ring, quinazoline ring, phthalazine ring, imidazole ring, isoxazole ring, pyrazole ring, oxazole ring, thiazole ring, indole ring, benzazole ring, benzothiazole ring, benzimidazole ring, benzofuran ring, furan ring, thiophene ring, pyrrole ring, oxadiazole ring, thiadiazole ring, triazole ring, tetrazole ring, pyrrole ring, indoline ring, indazole ring, isoindole ring, purine ring, morpholine ring, quinoxaline ring, benzothiophene ring, pyrrolidine ring, benzofurazane ring, benzothiadiazole ring, thiazolidine ring, imidazothiazole ring, dibenzofuran ring, and isothiazole ring.

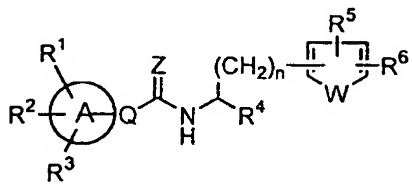
In the above formula (I), "aryl group" may be a mono-, bi- or tri-cyclic aromatic group. Examples of "aryl group" may be a phenyl group, a naphthyl group, an anthryl group and a fluorenyl ring.

In the above formula (I), "heterocyclic group" may be a mono-, bi- or tri-cyclic ring containing a heteroatom such as nitrogen atom, oxygen atom, and sulfur atom. Examples of "heterocyclic group" may be pyridyl group, pyrimidinyl group, pyridazinyl group, pyrazinyl group, quinolyl group, isoquinolyl group, quinazolinyl group, phthalazinyl group, imidazolyl group, isoxazolyl group, pyrazolyl group, oxazolyl group, thiazolyl group, indolyl group, benzazolyl group, benzothiazolyl group, benzimidazolyl group, benzofuranyl group, furyl group, thienyl group, pyrrolyl group, oxadiazolyl group, thiadiazolyl group, triazolyl group, tetrazolyl group, pyrrolyl group, indolinyl group, indazolyl group, isoindolyl group, purinyl group, morpholinyl group, quinoxalinyl group, benzothienyl group,

pyrrolidinyl group, benzofurazanyl group, benzothiadiazolyl group, thiazolidinyl group, imidazothiazolyl group, dibenzofuranyl group, isothiazolyl group, pyrrolinyl group, piperidinyl group, piperazinyl group, and tetrahydropyranyl group.

In the above formula (I), "heteroaryl group" may be a mono-, bi- or tri-cyclic aromatic group containing a heteroatom such as nitrogen atom, oxygen atom, and sulfur atom. Examples of "heteroaryl group" may be a "heterocyclic ring" other than pyrrolidinyl group, pyrrolinyl group, piperidinyl group, piperazinyl group, morpholinyl group, and tetrahydropyranyl group. Preferable examples of the "heteroaryl group" may be pyridyl group, thienyl group, benzofuranyl group, pyrimidyl group, and isoxazolyl group.

The novel compound among the compound [I] of the present invention is indicated as follows:



[I]

wherein

Ring A is an aromatic hydrocarbon ring or a heterocyclic ring;

Q is a bond, a carbonyl group, a lower alkylene group which may be substituted by a hydroxyl group or phenyl group, a lower alkenylene group, or a -O-(lower alkylene)-group;

n is an integer of 0, 1 or 2;

W is oxygen atom, sulfur atom, a -CH=CH- group or a -N=CH- group;

Z is oxygen atom or sulfur atom;

R^1, R^2 and R^3 are the same or different and are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a substituted or unsubstituted lower alkyl group,

d) a substituted or unsubstituted lower alkoxy group,

e) a nitro group,

f) a substituted or unsubstituted amino group,

g) a carboxyl group or an amide or an ester thereof,

h) a cyano group,

i) a lower alkylthio group,

j) a lower alkanesulfonyl group,

k) a substituted or unsubstituted sulfamoyl group,

l) a substituted or unsubstituted aryl group,

m) a substituted or unsubstituted heterocyclic group, and

n) hydroxyl group;

or two of R^1, R^2 and R^3 may combine each other at the terminal thereof to form a lower alkylenedioxy group;

R^4 is tetrazolyl group, a carboxyl group, or an amide or an ester thereof;

R^5 is a group selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) a substituted or unsubstituted amino group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a substituted or unsubstituted lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom, and

j) 2-oxopyrrolidinyl group;

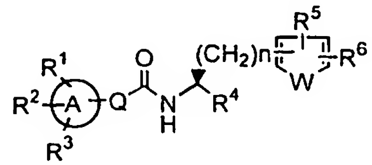
R^6 is a group selected from the group consisting of :

a) a substituted or unsubstituted phenyl group,

b) a substituted or unsubstituted heteroaryl group;

with the proviso that when Ring A is a benzene ring, the ring is not substituted with methyl group in the 3- and the 5-positions or in the 2- and the 4-positions;
or a pharmaceutically acceptable salt thereof.

A preferred configuration of the active ingredient of the present invention is represented by the formula [I-A]:



[I-A]

wherein symbols are the same as defined above.

A preferred embodiment of the present invention is the compound [I] with the additional proviso that when Ring A is a benzene ring, the ring is substituted in at least one of 2- and 6-positions.

Another preferred embodiment of the present invention is the compound (I) wherein R^1, R^2 and R^3 are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a substituted or unsubstituted lower alkoxy group,

d) a nitro group,

e) a substituted or unsubstituted amino group,

f) a carboxyl group or an amide or an ester thereof,

g) a cyano group,

h) a lower alkylthio group,

i) a lower alkanesulfonyl group,

j) a substituted or unsubstituted sulfamoyl group,

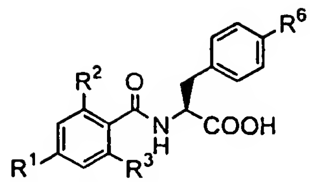
k) a substituted or unsubstituted aryl group,

l) a substituted or unsubstituted heterocyclic group, and

m) hydroxyl group,

or two of R^1, R^2 and R^3 may combine with each other at the terminal thereof to form a lower alkylenedioxy group.

A more preferred configuration of the active ingredient of the present invention is represented by the formula [I-B]:


[I-B]

wherein symbols are the same as defined above.

In more preferred embodiment of the present invention, R^1 is hydrogen atom, a halogen atom, carboxyl group, carbamoyl group, nitro group, a substituted or unsubstituted amino group, a substituted or unsubstituted heterocyclic ring;

R^2 is hydrogen atom, a lower alkyl group or a halogen atom;

R^3 is hydrogen atom, a lower alkyl group or a halogen atom;

R^6 is a phenyl group which may be substituted at 2-, 4-, and/or 6-position of the phenyl group by a group selected from the group consisting of:

1) a halogen atom,

2) a substituted or unsubstituted lower alkoxy group,

3) a substituted or unsubstituted lower alkyl group ,

4) a substituted or unsubstituted amino group,

5) a substituted or unsubstituted carbamoyl group, and

6) a substituted or unsubstituted sulfamoyl group.

In further preferred embodiment of the present invention, R^6 is a phenyl group which may be substituted by a group selected from the group consisting of:

1) a lower alkoxy group, and

2) a lower alkyl group which may be substituted by a group selected from a substituted or unsubstituted amino group, a substituted or unsubstituted piperidinyl group, a substituted or unsubstituted morpholino group, a substituted or unsubstituted piperazinyl group, a substituted or unsubstituted pyrrolidinyl group, and a substituted or unsubstituted imidazolidinyl group.

In another embodiment of the present invention,

Ring A is a benzene ring, a pyridine ring, a pyrazine ring, a furan ring, an isoxazole ring, a benzofuran ring, a thiophene ring, a pyrrole ring, or an indole ring;

R^1, R^2 and R^3 are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a lower alkyl group which may be substituted by a halogen atom or a (halogenobenzoyl)amino group,

d) a lower alkoxy group which may be substituted by a halogen atom,

e) a nitro group,

f) an amino group which may be substituted by 1-2 groups selected from the group consisting of 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a halogenobenzoyl group, 4) a lower alkoxycarbonyl group, 5) a lower alkanesulfonyl group which may be substituted by a halogen atom, 6) a benzenesulfonyl group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 7) thiophenesulfonyl group, 8) a carbamoyl group which may be substituted by a lower alkyl group, a lower alkyl-phenyl group, 9) a thiocarbamoyl group which may be substituted by a lower alkyl group, phenyl group, a phenyl-lower alkyl group, 10) thiazolinyl group, and 11) a sulfamoyl group which may be substituted by a lower alkyl group;

g) a carboxyl group,

h) a carbamoyl group which may be substituted by a lower alkanesulfonyl group,

i) a lower alkoxycarbonyl group,

j) a cyano group,

k) a lower alkylthio group,

l) a lower alkanesulfonyl group,

m) a sulfamoyl group,

n) a phenyl group,

o) a pyrrolidinyl group which may be substituted by oxo group,

p) a pyrrolyl group which may be substituted by a group selected from the group consisting of 1) a lower alkanoyl group which may be substituted by a halogen atom, 2) a halogen atom, 3) formyl group, and 4) a lower alkyl group which may be substituted by hydroxy group,

q) a thienyl group,

r) an isoxazolyl group which may be substituted by a lower alkyl group,

s) a thiazolyl group,

t) a pyrazolyl group,

u) a pyrazinyl group,

v) a pyridyl group, and

w) hydroxyl group;

R^4 is selected from the group consisting of:

a) carboxyl group,

b) a lower alkoxycarbonyl group which may be substituted by 1) pyridyl group or 2) an amino group which may be substituted by a lower alkyl group,

c) a lower cycloalkoxy carbonyl group,

d) a carbamoyl group which may be substituted by a hydroxy group or a lower alkanesulfonyl group, and

e) a tetrazolyl group;

R^5 is selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) an amino group which may be substituted by a lower alkanoyl group, a lower alkoxycarbonyl group or a lower alkanesulfonyl group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a lower alkyl group which may be substituted by 1) hydroxyl group, or 2) an imino group which is substituted by hydroxyl group or a lower alkoxy group,

g) a lower alkoxy group,

h) a halogen atom,

i) 2-oxopyrrolidinyl group;

R^6 is the group selected from the group consisting of :

a) a phenyl group which may have 1-5 substituents selected from the group consisting of:

1) a halogen atom,

2) a nitro group,

3) a formyl group,

4) a hydroxyl group,

5) a carboxyl group,

6) a lower alkoxy group which may be substituted by a group selected from the group consisting of i) a carboxyl group or an amide or an ester thereof, ii) hydroxyl group, iii) a cyano group, iv) a halogen atom, v) an amino group which may be substituted by a lower alkyl group, vi) a pyridyl group, vii) a thiazolyl group which may be substituted by a lower alkyl group, viii) an isoxazolyl group which may be substituted by a lower alkyl group, ix) a piperidyl group which may be substituted by a lower alkyl group, x) a pyrrolidinyl group which may be substituted by a lower alkyl group, xi) a phenyl group which may be substituted by a halogen atom, xii) a furyl group, xiii) a thienyl group, and xiv) a lower alkoxy group

7) a lower alkyl group which may be substituted by a group selected from the group consisting of i) a halogen atom, ii) hydroxyl group, iii) carboxyl group or an amide or an ester thereof, iv) a lower alkoxy group, v) an amino group which may be substituted by

1-2 groups selected from the group consisting of a lower alkyl group, a hydroxy-lower alkyl group, a (lower alkylamino)-lower alkyl group, phenyl-lower alkyl group, a phenyl group, and a pyridyl group, vi) a piperidinyl group which may be substituted by a lower alkylenedioxy group, an oxo group or a hydroxy group, vii) a morpholino group which may be substituted by a lower alkyl group, viii) thiomorpholino group which may be oxidized, ix) piperazinyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a lower alkanoyl group or a phenyl-lower alkyl group, x) pyrrolidinyl group which may be substituted by oxo group, and xi) a imidazolidine group which may be substituted by 1-3 groups selected from the group consisting of a lower alkyl group and oxo group,

8) a lower alkenyl group which may be substituted by carboxyl group or an amide or an ester thereof,

9) an amino group which may be substituted by a group selected from the group consisting of i) a phenyl group, ii) a lower alkoxycarbonyl group, iii) a lower alkanesulfonyl group, iv) a carbamoyl group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, v) a lower alkanoyl group, vi) a lower alkyl group, vii) a lower alkenyl group, and viii) a thiocarbamoyl group which may be substituted by a lower alkyl group,

10) a carbamoyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a morpholino-lower alkyl group, a phenyl-lower alkyl group or a lower alkanesulfonyl group,

11) a sulfamoyl group which may be substituted by a group consisting of i) a lower alkyl group, ii) a benzoyl group, iii) a lower alkoxycarbonyl group, and iv) a lower alkanoyl group,

12) a lower alkenyloxy group,

13) a lower alkylenedioxy group,

14) a piperazinylcarbonyl group which may be substituted by a lower alkyl group,

15) a lower alkanoyl group,

16) cyano group,

17) a lower alkylthio group,

18) a lower alkanesulfonyl group,

19) a lower alkylsulfinyl group, and

20) a group of the formula: $-(CH_2)_q-O-$,

wherein q is an integer of 2 or 3;

b) a pyridyl group which may be substituted by a lower alkyl group;

c) a thienyl group which may be substituted by a group selected from the group consisting of:

1) a halogen atom,

2) a lower alkyl group which may be substituted by hydroxyl group,

3) cyano group,

4) formyl group,

5) a lower alkoxy group, and

6) a lower alkanoyl group;

d) a benzofuranyl group;

e) a pyrimidinyl group which may be substituted by a lower alkoxy group;

f) a isoxazolyl group which may be substituted by a lower alkyl group; and

g) a pyrrolyl group which may be substituted by a lower alkoxycarbonyl group.

In preferred embodiment of the present invention,

Ring A is a benzene ring,

Q is a bond,

W is a -CH=CH- group,

R^1 is selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a lower alkyl group,

d) a lower alkoxy group,

e) nitro group,

f) an amino group which may be substituted by a group selected from the group consisting of 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a lower alkoxycarbonyl group, 4) a lower alkanesulfonyl group which may be substituted by a halogen atom, 5) a benzenesulfonyl group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 6) thiophenesulfonyl group, 7) a carbamoyl group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, 8) a thiocarbamoyl group which may be substituted by a lower alkyl group, and 9) a sulfamoyl group which may be substituted by a lower alkyl group,

g) carboxyl group

h) a carbamoyl group which may be substituted by a lower alkanesulfonyl group,

i) a lower alkanesulfonyl group,

j) a sulfamoyl group,

k) phenyl group,

l) a pyrrolidinyl group which may be substituted by oxo group,

l) a pyrrolyl group which may be substituted by a lower alkyl group,

m) a thienyl group,

n) an isoxazolyl group which may be substituted by a lower alkyl group,

o) a thiazolyl group

p) a pyrazolyl group,

q) a pyrazinyl group,

r) a pyridyl group, and

s) hydroxyl group;

R^2 is hydrogen atom, or a halogen atom;

R^3 is hydrogen atom, or a halogen atom;

R^4 is a) a carboxyl group,

b) a lower alkoxycarbonyl group which may be substituted by a lower alkyl-amino group, or

c) a carbamoyl group which may be substituted by a lower alkanesulfonyl group;

R^5 is selected from the group consisting of:

a) hydrogen atom,

b) an amino group which may be substituted by a lower alkanoyl group, a lower alkoxycarbonyl group or a lower alkanesulfonyl group,

c) a lower alkanoyl group,

d) a lower alkyl group which may be substituted by 1) hydroxyl group, or 2) an imino group which is substituted by hydroxyl group or a lower alkoxy group,

e) a lower alkoxy group, and

f) a halogen atom;

R^6 is a phenyl group which may have 1-5 substituents selected from the group consisting of:

a) a halogen atom,

b) a formyl group,

c) a hydroxyl group,

d) a lower alkoxy group which may be substituted by 1) a carboxyl group, 2) a hydroxyl group, 3) a cyano group, 4) a halogen atom, 5) an amino group which may be substituted by a lower alkyl group, 6) a pyridyl group, 7) a phenyl group, 8) a thienyl group, or 9) a lower alkoxy group,

e) a lower alkyl group which may be substituted by 1) an amino group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a lower alkylamino-lower alkyl group or a phenyl group, 2) a piperidinyl group

which may be substituted by a lower alkylenedioxy group, 3) a morpholino group which may be substituted by a lower alkyl group, 4) a thiomorpholino group in which sulfur atom may be oxidized, 5) a piperazinyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a lower alkanoyl group or a phenyl-lower alkyl group, 6) pyrrolidinyl group which may be substituted by oxo group, or 7) an imidazolidinyl group which may be substituted by 1-3 groups selected from the group consisting of a lower alkyl group and oxo group,

f) an amino group which may be substituted by 1) a lower alkoxycarbonyl group, 2) a lower alkanesulfonyl group, 3) a carbamoyl group which may be substituted by a lower alkyl group a lower alkyl-phenyl group, 4) a lower alkanoyl group, 5) a lower alkyl group, 6) a lower alkenyl group, or 7) a thiocarbamoyl group which may be substituted by a lower alkyl group,

g) a carbamoyl group which may be substituted by 1) a lower alkyl group, 2) a hydroxy-lower alkyl group, 3) a morpholino-lower alkyl group, 4) a phenyl-lower alkyl group, or 5) a lower alkanesulfonyl group,

h) a sulfamoyl group which may be substituted by a lower alkyl group,

i) a lower alkenyloxy group,

j) a lower alkylenedioxy group,

k) a cyano group,

l) a lower alkylthio group, and

m) a lower alkanesulfonyl group.

In more preferred embodiment of the present invention, R^1 is 1) hydrogen atom, 2) a halogen atom, 3) a lower alkanoylamino group, 4) a lower alkoxycarbonylamino group, 5) a lower alkanesulfonylamino group which may be substituted by a halogen atom, 6) a benzenesulfonylamino group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower

alkoxy group, 7) thiophenesulfonylamino group, 8) an ureido group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, 9) a lower alkyl-thioureido group, or 10) a lower alkylsulfamoylamino group, R^2 is a halogen atom, R^3 is hydrogen atom or a halogen atom, and R^6 is a phenyl group which may have 1-3 substituents selected from the group consisting of 1) a lower alkoxy group, 2) a lower alkyl group which may be substituted by a group selected from the group consisting of a lower alkylamino group, a hydroxy-lower alkylamino group, a lower alkylamino-lower alkylamino group, piperidinyl group, a lower alkyl-piperidinyl group, morpholino group, a lower alkyl-morpholino group, a thiomorpholino group, piperazinyl group, a lower alkyl-piperazinyl group, a lower alkanoyl-piperazinyl group, and a pyrrolidinyl group, 3) a sulfamoyl group which may be substituted by a lower alkyl group, 4) a carbamoyl group which may be substituted by a lower alkyl group.

In another more preferred embodiment of the present invention, R^1 is hydrogen atom, R^3 is a halogen atom, and R^6 is 2-(lower alkoxy)phenyl group, 2,6-di(lower alkoxy)phenyl group, 2,6-di(lower alkoxy)-4-[[N,N-di(lower alkyl)amino]lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[(4-lower alkyl-1-piperazinyl)lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[1-piperidinyl-lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[N, N-di(lower alkyl)-carbamoyl]phenyl group or 2,6-di(lower alkoxy)-4-[(morpholino)lower alkyl]phenyl group.

In another more preferred embodiment of the present invention, a lower alkoxy group is methoxy group.

Preferred compounds as the active ingredient of the present invention may be selected from the group consisting of:

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(piperidinomethyl)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-methylpiperazinyl)amino]phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N,N-dimethylamino)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N, N-dimethylcarbamoyl)phenyl]-L-phenylalanine;

N-(2,6-dichloro-4-hydroxybenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2-ethoxy-6-methoxyphenyl)-L-phenylalanine;

N-(2,6-difluorobenzoyl)-4-(2-6,dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2,3-methylenedioxy-6-methoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethy)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2,4,6-trimethoxyphenyl)-L-phenylalanine;

N-[2,6-dichloro-4-[(trifluoromethanesulfonyl)amino]-benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine; or

N-[2,6-dichloro-4-[(2-thienylsulfonyl)amino]benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

or a lower alkyl ester such as ethyl ester thereof;

or pharmaceutically acceptable salt thereof.

The active ingredient of the present invention may be used in the form of an ester or amide thereof. As the ester thereof, there may be mentioned a) a lower alkyl ester which may be substituted by 1) pyridyl group, 2) an amino group which may be substituted by a lower alkyl group, 3) a lower alkanoyloxy group, 4) an aryl group; b) a lower alkenyl ester; c) a lower alkynyl ester; d) a lower cycloalkyl ester; e) an aryl ester. As the amide thereof, there may be mentioned an amide ($-CONH_2$) which may be substituted by 1) a lower alkyl group, a lower cycloalkyl group, aryl group, aryl-lower alkyl group, hydroxy group or a lower alkanesulfonyl group;

An ester of the formula [I] includes, for example, an ester which can be converted to the corresponding carboxylic acid in a body, for example, a lower alkyl ester (e.g., methyl ester), a lower alkanoyloxy-lower alkyl ester (e.g., acetoxymethyl ester) and the like. An amide of the formula [I] includes, for example, an N-unsubstituted amide, an N-monosubstituted amide (e.g., an N-lower alkyl amide), an N,N-disubstituted amide (e.g., an N,N-(lower alkyl) (lower alkyl) amide) and the like.

A pharmaceutically acceptable salt of the formula [I] includes, for example, a salt with an inorganic acid (e.g., hydrochloride, sulfate), a salt with an organic acid (e.g., p-toluenesulfonate, maleate), a salt with an inorganic base (e.g., a salt with an alkali metal such as a sodium salt or a potassium salt) or a salt with an amine (e.g., an ammonium salt).

The active ingredient of the present invention may be used either in a free form or in the form of pharmaceutically acceptable salts thereof. Pharmaceutically acceptable salts include acid-addition salts with inorganic acid or organic acid (e.g., hydrochloride, sulfate, nitrate, hydrobromide, methanesulfonate, p-toluenesulfonate, acetate), salt with

inorganic base, organic base or amino acid (e.g., triethylamine salt, a salt with lysine, an alkali metal salt, an alkali earth metal, salt and the like).

The active ingredient may be formulated into a pharmaceutical composition comprising a therapeutically effective amount of the compound as defined above and a pharmaceutically acceptable carrier or diluent.

The composition can be used for treating or preventing α_4 (including $\alpha_4\beta_1$ and $\alpha_4\beta_7$ adhesion mediated conditions in a mammal such as a human, especially used for treatment or prevention of $\alpha_4\beta_7$ adhesion mediated conditions. This method may comprise administering to a mammal or a human patient an effective amount of the compound or composition as explained above.

This method can be used to treat or prevent such inflammatory conditions as rheumatoid arthritis, asthma, psoriasis, eczema, contact dermatitis and other skin inflammatory diseases, diabetes, multiple sclerosis, systemic lupus erythematosus (SLE), inflammatory bowel disease including ulcerative colitis and Crohn's disease, and other diseases involving leukocyte infiltration of the gastrointestinal tract, or other epithelial lined tissues, such as skin, urinary tract, respiratory airway, and joint synovium. The method can be preferably used for treatment or prevention of inflammatory bowel disease including ulcerative colitis and Crohn's disease.

The present invention also relates to a method for inhibiting the interaction of a cell bearing a ligand of MAdCAM-1, including $\alpha4\beta7$ integrins, with MAdCAM-1 or a portion thereof (e.g., the extracellular domain), comprising contacting the cell with an active ingredient of the present invention. In one embodiment, the present invention relates to a method of inhibiting the MAdCAM-mediated interaction of a first cell bearing an $\alpha4\beta7$

integrin with MAdCAM, for example with a second cell bearing MAdCAM, comprising contacting the first cell with an active ingredient of the present invention. In another embodiment, the invention relates to a method of treating an individual suffering from a disease associated with leukocyte recruitment to tissues (e.g., endothelium) expressing the molecular MAdCAM-1.

Another embodiment of the present invention is a method of treating an individual suffering from a disease associated with leukocyte infiltration of tissues expressing the molecule MAdCAM-1.

According to the present method, the cell bearing the ligand for MAdCAM-1 is contacted with an effective amount of an (i.e., one or more) inhibitor as represented by Structural Formula [I]. As used herein, an inhibitor is a compound which inhibits (reduces or prevents) the binding of MAdCAM-1 to a ligand, including $\alpha4\beta7$ integrin, and/or which inhibits the triggering of a cellular response mediated by the ligand. An effective amount can be an inhibitory amount (such an amount sufficient to achieve inhibition of adhesion of a cell bearing a MAdCAM-1 ligand to MAdCAM-1). Ligands for MAdCAM-1 include $\alpha4\beta7$ integrins, such as human $\alpha4\beta7$ integrin, and its homologs from other species such as mice (also referred to as $\alpha4\beta p$ or LPAM-1 in mice).

For example, the adhesion of a cell which naturally expresses a ligand for MAdCAM-1, such as a leukocyte (e.g., B lymphocyte, T lymphocyte) or other cells which express a ligand for MAdCAM-1 (e.g., a recombinant cell), to MAdCAM-1 can be inhibited *in vitro* and/or *in vivo* according to the present method.

In another aspect, the present invention relates to a method of treating an individual (e.g., a mammal, such as a human or other primate) suffering from a disease associated

with leukocyte (e.g., lymphocyte, monocyte) infiltration of tissues (including recruitment and/or accumulation of leukocytes in tissues) which express the molecule MAdCAM-1. The method comprises administering to the individual a therapeutically effective amount of an inhibitor (i.e., one or more inhibitors) of Structural Formula [I]. For example, inflammatory diseases, including diseases which are associated with leukocyte infiltration of the gastrointestinal tract (including gut-associated endothelium), other mucosal tissues, or tissues expressing the molecular MAdCAM-1 (e.g., gut-associated tissues, such as venules of the lamina propria of the small and large intestine; and mammary gland (e.g., lactating mammary gland)), can be treated according to the present method. Similarly, an individual suffering from a disease associated with leukocyte infiltration of tissues as a result of binding of leukocytes to cells (e.g., endothelial cells) expressing the molecule MAdCAM-1 can be treated according to the present invention.

Diseases which can be treated accordingly include inflammatory bowel disease (IBD), such as ulcerative colitis, Crohn's disease and pouchitis resulting after proctocolectomy and ileoanal anastomosis after IBD; and other gastrointestinal diseases associated with leukocyte infiltration, such as Celiac disease, nontropical Sprue, enteropathy associated with seronegative arthropathies, lymphocytic and graft versus host diseases.

Pancreatitis and insulin-dependent diabetes mellitus are other diseases which can be treated using the present method. It has been reported that MAdCAM-1 is expressed by some vessels in the exocrine pancreas from NOD (nonobese diabetic) mice, as well as from BALB/c and SJL mice. Expression of MAdCAM-1 was reportedly induced on endothelium in inflamed islets of the pancreas of the NOD mouse, and MAdCAM-1 was the predominant address in

expressed by NOD islet endothelium at early stages of insulitis (Hanninen, A. et al., J. Clin. Invest., 92: 2509-2515 (1993)). Further, accumulation of lymphocytes expressing α4β7 within islets was observed, and MAdCAM-1 was implicated in the binding of lymphoma cells via α4β7 to vessels from inflamed islets (Hanninen, A., et al., J. Clin. Invest., 92: 2509-2515 (1993)).

Examples of inflammatory diseases associated with mucosal tissues which can be treated according to the present method include mastitis (mammary gland), cholecystitis, cholangitis or pericholangitis (bile duct and surrounding tissue of the liver), chronic bronchitis, chronic sinusitis, asthma, and graft versus host disease (e.g., in the gastrointestinal tract). Chronic inflammatory diseases of the lung which result in interstitial fibrosis, such as hypersensitivity pneumonitis, collagen disease (in SLE and RA), sarcoidosis, and other idiopathic conditions can be amenable to treatment.

Vascular cell adhesion molecule-1 (VCAM-1), which recognizes the α4β1 integrin (VLA-4), has been reported to play a role in *in vivo* leukocyte recruitment (Silber et al., J. Clin. Invest. 93:1554-1563 (1994)). However, these therapeutic targets are likely to be involved in inflammatory processes in multiple organs, and a functional blockade could cause systemic immune dysfunction. In contrast to VCAM-1, MAdCAM-1 is preferentially expressed in the gastrointestinal tract and mucosal tissues, binds the α4β7 integrin found on lymphocytes, and participates in the homing of these cells to mucosal sites, such as Peyer's patches in the intestinal wall (Hamann et al., J. Immunol., 152:3282-3293 (1994)). As inhibitors of the binding of MAdCAM-1 to α4β7 integrin, the active ingredients of the present invention have the potential for fewer side effects

due to, for example, effects on other tissue types where adhesion is mediated by other receptors, such as α4β1 integrin.

Undesired symptoms of the condition listed herein can alleviated using the present method. The symptoms may be caused by inappropriate cell adhesion and/or cell activation to release proinflammatory mediators mediated by α4β7 integrins. Such inappropriate cell adhesion or signal transduction would typically be expected to occur as a result of increased VCAM and/or MAdCAM expression on the surface of endothelial cells. Increased VCAM, MAdCAM and/or CS-1 expression can be due to a normal inflammatory response or due to abnormal inflammatory states.

The present method can be used to assess the inhibitory effect of a compound of the present invention and of other potential antagonists useful in the method on the interaction of MAdCAM-1 with a ligand for MAdCAM-1 *in vitro* or *in vivo*.

Compounds suitable for use in therapy can also be evaluated *in vivo*, using suitable animal models. Suitable animal models of inflammation have been described. For example, NOD mice provide animal model of insulin-dependent diabetes mellitus. CD45 RB^{Hi} SCID model provide a model in mice with similarity to both Crohn's disease and ulcerative colitis (Powrie, F. et al., Immunity, 1: 553-562 (1994)). Captive cotton-top tamarins, a New World nonhuman primate species, develop spontaneous, often chronic, colitis that clinically and histolgocially resembles ulcerative colitis in humans (Madara, J.L. et al., Gastroenterology, 88: 13-19 (1985)). The tamarin model and other animal models of gastrointestinal inflammation using BALB/c mice (a (DSS)-induced inflammation model; DSS, dextran sodium sulfate). IL-10 knockout mice which develop intestinal lesions similar to those of human inflammatory bowel disease have

also been described (Strober, W. and Ehrhardt, R.O., Cell, 75: 203-205 (1993)).

According to the method, an inhibitor can be administered to an individual (e.g., a human) alone or in conjunction with another agent, such as an additional pharmacologically active agent (e.g., sulfasalazine, an antiinflammatory compound, or a steroidal or other nonsteroidal antiinflammatory compound). A compound can be administered before, along with or subsequent to administration of the additional agent, in amounts sufficient to reduce or prevent MAdCAM-mediated binding to a ligand for MAdCAM-1, such as human $\alpha_4\beta_7$.

An effective amount of the active ingredient can be administered by an appropriate route in a single dose or multiple doses. An effective amount is a therapeutically effective amount sufficient to achieve the desired therapeutic and/or prophylactic effect (such as an amount sufficient to reduce or prevent MAdCAM-mediated binding to a MAdCAM ligand, thereby inhibiting leukocyte adhesion and infiltration and associated cellular responses. Suitable dosages of active ingredient of the present invention for use in therapy, diagnosis or prophylaxis, can be determined by methods known in the art and can be dependent, for example, upon the individual's age, sensitivity, tolerance and overall well-being.

The active ingredient of the present invention or pharmaceutically acceptable salts thereof may be administered either orally or parenterally, and it may be used as a suitable pharmaceutical preparation, for example, a tablet, a granule, a capsule, a powder, an injection, and an inhalation by a conventional process.

The dose of the active ingredient of the present invention or a pharmaceutically acceptable salt thereof varies depending on an administration method, age, body weight, and state of a patient, but, in general, the daily

dose is preferably about 0.1 to 100 mg/kg/day, particularly preferably 1 to 100 mg/kg/day.

Pharmaceutical Compositions

As indicated previously, the active ingredient of formula [I] can be formulated into pharmaceutical compositions. In determining when a compound of formula [I] is indicated for the treatment of a given disease, the particular disease in question, its severity, as well as the age, sex, weight, and condition of the subject to be treated, must be taken into consideration and this perusal is to be determined by the skill of the attendant physician.

For medical use, the amount of a compound of Formula [I] required to achieve a therapeutic effect will, of course, vary both with the particular compound, the route of administration, the patient under treatment, and the particular disorder or disease being treated. A suitable daily dose of a compound of Formula [I], or a pharmaceutically acceptable salt thereof, for a mammalian subject suffering from, or likely to suffer from, any condition as described herein before is 0.1 mg to 100 mg of the compound of formula [I], per kilogram body weight of the (systemic) mammalian subject. In the case of systemic administration, the dose may be in the range of 0.5 to 100 mg of the compound per kilogram body weight, the most preferred dosage being 0.5 to 50 mg/kg of mammal body weight administered two to three times daily. In the case of topical administration, e.g., to the skin or eye, a suitable dose may be in the range of 0.1 μg to 100 μg of the compound per kilogram, typically about 0.1 μg/kg.

In the case of oral dosing, a suitable dose of a compound of Formula [I], or a physiologically acceptable salt thereof, may be as specified in the preceding paragraph, but preferably is from 1 mg to 50 mg of the compound per kilogram, the most preferred dosage being from

5 mg to 25 mg/kg of mammal body weight, for example, from 1 to 10 mg/kg. Most preferably, a unit dosage of an orally administrable composition encompassed by the present invention contains less than about 1.0 g of a formula [I] compound.

It is understood that the ordinarily skilled physician or veterinarian will readily determine and prescribe the effective amount of a compound of Formula [I] to prevent or arrest the progress of the condition for which treatment is administered. In so proceeding, the physician or veterinarian could employ relatively low doses at first, subsequently increasing the dose until a maximum response is obtained.

The compounds and compositions of the present invention can be administered to patients suffering from a condition listed herein in an amount which is effective to fully or partially alleviate undesired symptoms of the condition. The symptoms may be caused by inappropriate cell adhesion or cell activation to release proinflammatory mediators mediated by $\alpha_4\beta_7$ integrins. Such inappropriate cell adhesion or signal transduction would typically be expected to occur as a result of increased VCAM-1 and/or MAdCAM expression on the surface of endothelial cells. Increased VCAM-1, MAdCAM and/or CS-1 expression can be due to a normal inflammation response or due to abnormal inflammatory states. In either case, an effective dose of a compound of the invention may reduce the increased cell adhesion due to increased VCAM-1 and/or MAdCAM expression by endothelial cells. Reducing the adhesion observed in the disease state by 50% can be considered an effective reduction in adhesion. More preferably, a reduction in *ex vivo* adhesion by 90%, is achieved. Most preferably, adhesion mediated by VCAM-1, MAdCAM and/or CS-1 interaction is abolished by an effective dose. Clinically, in some instances, effect of the compound can be observed as a decrease in white cell infiltration

into tissues or a site of injury. To achieve a therapeutic effectiveness, then, the compounds or compositions of the present invention are administered to provide a dose effective to reduce or eliminate inappropriate cell adhesion or inappropriate cell activation to alleviate undesired symptoms.

While it is possible for an active ingredient to be administered alone, it is preferable to present it as a pharmaceutical formulation comprising a compound of Formula [I] and a pharmaceutically acceptable carrier thereof. Such formulations constitute a further feature of the present invention.

The formulations, both for human and veterinary medical use, of the present invention comprise an active ingredient of Formula [I], in association with a pharmaceutically acceptable carrier thereof and optionally other therapeutic ingredient(s), which are generally known to be effective in treating the disease or condition encountered. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulations and not deleterious to the recipient thereof.

The formulations include those in a form suitable for oral, pulmonary, ophthalmic, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), intra-articular, topical, nasal inhalation (e.g., with an aerosol) or buccal administration. Such formulation are understood to include long-acting formulations known in the art. Oral and parenteral administration are preferred modes of administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods may include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by

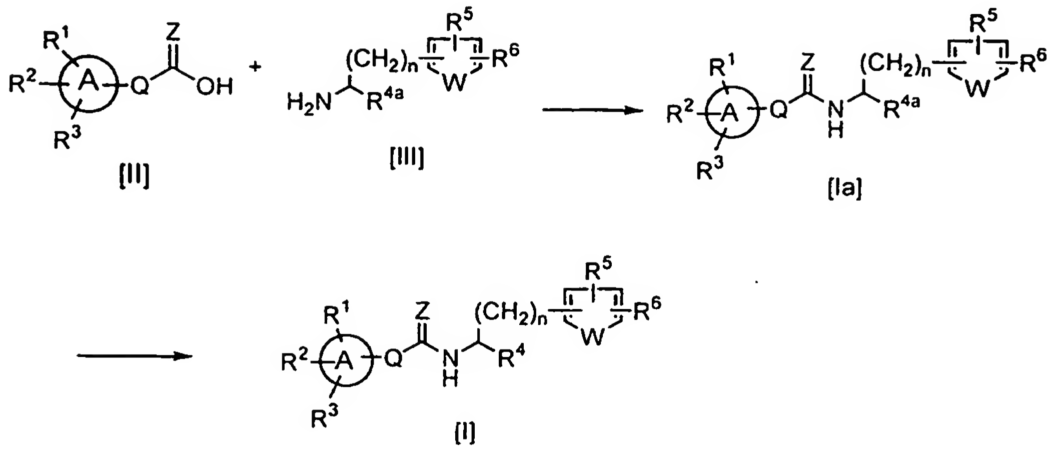
uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired form.

Formulations of the present invention suitable for oral administration may be in the form of discrete units such as capsules, cachets, tablets, or lozenges, each containing a predetermined amount of the active ingredient in the form of a powder or granules; in the form of a solution or suspension in an aqueous liquid. Formulations for other uses could involve a nonaqueous liquid; in the form of an oil-in-water emulsion or a water-in-oil emulsion; in the form of an aerosol; or in the form of a cream or ointment or impregnated into a transdermal patch for use in administering the active ingredient transdermally, to a patient in need thereof. The active ingredient of the present inventive compositions may also be administered to a patient in need thereof in the form of a bolus, electuary, or paste.

The practitioner is referred to "Remington: The Science and Practice of Pharmacy," 19^{th} Edition, c. 1995 by the Philadelphia College of Pharmacy and Science, as a comprehensive tome on pharmaceutical preparations.

According to the present invention, the novel compound [I] can be prepared by the following methods.

<u>Method A:</u>



(wherein R^{4a} is an ester group, and other symbols are the same as defined above)

The compound of the formula [I] or a pharmaceutically acceptable salt thereof may be prepared by :

(1) condensing a compound of the formula [II], a salt thereof or a reactive derivative thereof with a compound of the formula [III] or a salt thereof,

(2) converting the ester group of the compound of the formula [Ia] into a carboxyl group, if desired, and

(3) converting the carboxyl group of the resulting compound into an ester group, an amide group , a tetrazolyl group or a pharmaceutically acceptable salt thereof, if further desired.

A salt of the compound [II] and/or [III] includes, for example, a salt with an inorganic acid (e.g., trifluoroacetate, hydrochloride, sulfate), a salt with an inorganic base (e.g., an alkali metal salt such as a sodium salt or a potassium salt, an alkaline earth metal salt such as a barium salt or calcium salt).

(1) The condensation reaction can be carried out by a conventional method for a usual amide bond synthesis.

The condensation reaction of the compound [II] or a salt thereof with the compound [III] or a salt thereof is carried out in the presence of a condensing reagent with or without a base in a suitable solvent or without a solvent.

The condensing reagent can be selected from any one which can be used for a conventional amide bond synthesis, for example, BOP-Cl, BOP reagent, DCC, EDC or CDI.

The base can be selected from an organic base (e.g., DIEA, DMAP, DBU, Et_3N), an alkali metal hydride (e.g., NaH, LiH), an alkali metal carbonate (e.g., Na_2CO_3, K_2CO_3), an alkali metal hydrogen carbonate (e.g., $NaHCO_3$, $KHCO_3$), an alkali metal amide (e.g., $NaNH_2$), an alkali metal alkoxide (e.g., NaOMe, KOMe), a lower alkyl alkali metal salt(e.g., n-BuLi, t-BuLi), an alkali metal hydroxide (e.g., NaOH, KOH), an alkaline earth metal hydroxide (e.g., $Ba(OH)_2$), and the like.

The solvent can be selected from any one which does not disturb the condensation reaction, for example, CH_2Cl_2, THF, DMF or a mixture thereof. The reaction is carried out at a temperature of 0 °C to room temperature, preferably at room temperature.

The condensation reaction of the compound [III] or a salt thereof with the reactive derivative of the compound [II], for example, with an acid halide (e.g., an acid chloride), a reactive ester (e.g., an ester with p-nitrophenol), an anhydride thereof, a mixed anhydride with other carboxylic acid (e.g., a mixed anhydride with acetic acid), and the like, is carried out in the presence of a base or without a base in a solvent or without a solvent.

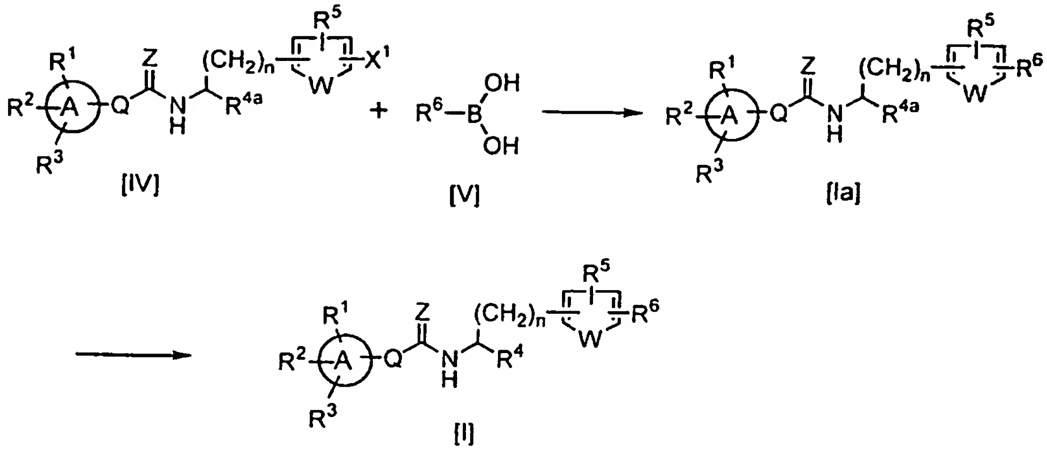
The base can be selected from an organic base (e.g., DIEA, DMAP, DBU, Et_3N), an alkali metal hydride (e.g., NaH, LiH), an alkali metal carbonate (e.g., Na_2CO_3, K_2CO_3), an alkali metal hydrogen carbonate (e.g., $NaHCO_3$, $KHCO_3$), an alkali metal amide (e.g., $NaNH_2$), an alkali metal alkoxide (e.g., NaOMe, KOMe), a lower alkylalkali metal salt(e.g., n-BuLi, t-BuLi), an alkali metal hydroxide (e.g., NaOH, KOH), an alkaline earth metal hydroxide (e.g., $Ba(OH)_2$), and the like.

The solvent can be selected from any one which does not disturb the condensation reaction, for example, CH_2Cl_2, $C_2H_4Cl_2$, Et_2O, THF, DMF, CH_3CN, DMSO, benzene, toluene or a mixture thereof. The reaction is carried out at a temperature of -30 °C to 100 °C.

(2) The conversion of the ester group into a carboxyl group can be carried out by a conventional method, which is selected according to the type of the ester group to be removed, for example, hydrolysis using a base (e.g., LiOH, NaOH) or an acid (e.g., HCl), treatment with an acid (e.g., TFA), catalytic reduction using a catalyst (e.g., palladium on activated carbon) and the like. The ester group can be selected from a conventional ester, for example, a lower alkyl ester, a lower alkenyl ester, a lower alkynyl ester, an aryl-lower alkyl ester (e.g., benzyl ester), an aryl ester (e.g., phenyl ester) and the like.

(3) The conversion of the carboxyl group into an ester group, an amide group or tetrazolyl group or conversion of the compound into a pharmaceutically acceptable salt thereof can be carried out by a conventional method. Particularly, the conversion of the carboxyl group into an ester group or an amide group can be carried out in a similar manner as described in Method A-(1). The conversion of the carboxyl group into tetrazolyl group is detailed in Procedure N below.

Method B:



(wherein X^1 is a leaving group and other symbols are the same as defined above.)

The compound of the formula [I] can be prepared by:

(1) reacting a compound of the formula [IV] with a compound of the formula [V],

(2) converting the ester group of the compound of the formula [Ia] into a carboxyl group, if desired, and

(3) converting the carboxyl group of the resulting compound into an ester group, an amide group, a tetrazolyl group or a pharmaceutically acceptable salt thereof, if further desired.

Examples of the leaving group X^1 may be a halogen atom and a trifluoromethanesulfonyloxy group.

(1) The coupling reaction can be carried out by a conventional aryl coupling method, e.g., Suzuki coupling method (for reference of Suzuki coupling method: (a) Suzuki et al., *Synth. Commun.* **1981**, *11*, 513, (b) Suzuki, *Pure and Appl. Chem.* **1985**, *57*, 1749-1758, (c) Suzuki et al., *Chem. Rev.* **1995**, *95*, 2457-2483, (d) Shieh et al., *J. Org. Chem.* **1992**, *57*, 379-381), (e) Martin et al., *Acta Chemica Scandinavica*, **1993**, *47*, 221-230.)

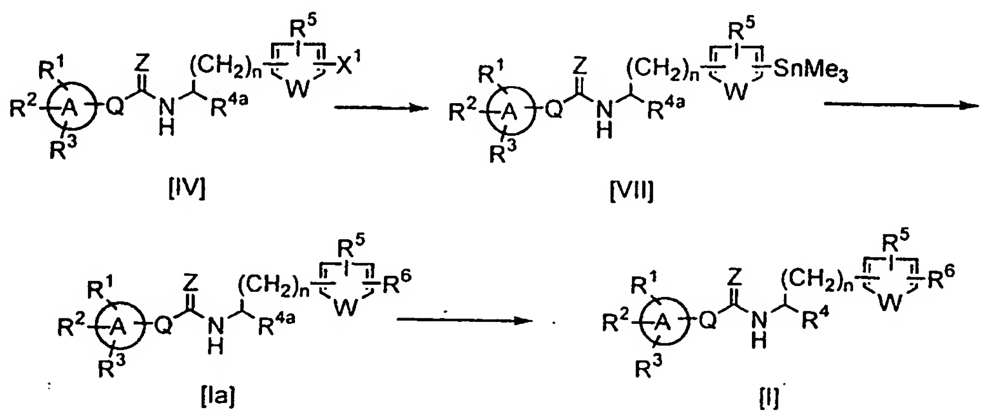
The coupling reaction can be carried out, for example, at a temperature of room temperature to 100 °C, preferably

at a temperature of 80 °C to 100 °C, in the presence of tetrakis(triphenylphosphine)palladium and a base (e.g., an inorganic base such as K_2CO_3) in an organic solvent. The organic solvent can be selected from any one which does not disturb the coupling reaction, for example, toluene, DME, DMF, H_2O or a mixture thereof.

(2) The conversion of ester group into carboxyl group can be carried out according to Method A-(2).

(3) The conversion of carboxyl group into ester group or amide group, a tetrazolyl group or pharmaceutically acceptable salt can be carried out according to Method A-(3).

Method C:



(wherein symbols are the same as defined above.)

The compound of the formula [I] can be also prepared by:

(1) converting the compound [IV] to the corresponding organotin compound (e.g., the compound of the formula [VII]),

(2) reacting the compound [VII] with a compound of the formula [VIII]:

R^6-X [VIII]

wherein X is a leaving group and R^6 is the same as defined above,

(3) converting the ester group of the compound of the formula [Ia] into a carboxyl group, if desired, and

(4) converting the carboxyl group of the resulting compound into an ester group, an amide group, a tetrazolyl group or a pharmaceutically acceptable salt thereof, if further desired.

Examples of the leaving group X is a halogen atom and a trifluoromethanesulfonyloxy group.

(1) The conversion of the compound [IV] to the organotin compound [VII] can be carried out, for example, by reacting the compound [IV] with hexaalkylditin (e.g., hexamethylditin) at a temperature of room temperature to 150 °C, preferably at a temperature of 80 °C to 110°C, in the presence of tetrakis(triphenylphosphine)palladium and an additive (e.g., LiCl) in an organic solvent. The organic solvent can be selected from any one which does not disturb the coupling reaction, for example, dioxane, toluene, DME, DMF, H_2O or a mixture thereof.

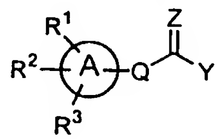
(2) The coupling reaction can be carried out by a conventional aryl coupling method, e.g., Stille coupling method (for reference of Stille coupling method: Stille et al., *Angew. Chem. Int. Ed. Engl.*, **25**, 508 (1986))

The coupling reaction can be carried out, for example, at a temperature of room temperature to 150 °C, preferably at a temperature of 80°C to 120 °C, in the presence of tetrakis(triphenylphosphine)palladium in an organic solvent. The organic solvent can be selected from any one which does not disturb the coupling reaction, for example, toluene, DME, DMF, H_2O or a mixture thereof.

(3) The conversion of ester group into carboxyl group can be carried out according to Method A-(2).

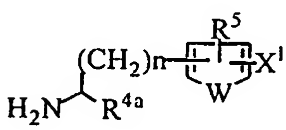
(4) The conversion of carboxyl group into ester group or amide group, a tetrazolyl group or pharmaceutically acceptable salt can be carried out according to Method A-(3).

The compound [IV] may be prepared by condensing the compound of the formula [IIa]:



[IIa]

wherein Y is a halogen atom and the other symbols are the same as defined above, with the compound of the formula [IIIa]:

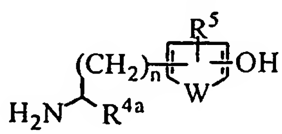


[IIIa]

wherein the symbols are the same as defined above or a salt thereof by the conventional method for the usual peptide synthesis as described above for the condensation reaction of the compound [III] or a salt thereof with the reactive derivative of the compound [II] (e.g., an acid halide).

The compound [IV] may be also prepared by :

(1) condensing the compound [IIa] with the compound of the formula [IIIb]:



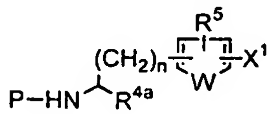
[IIIb]

wherein the symbols are the same as defined above or a salt thereof by the similar manner as described above,

(2) converting the hydroxyl group of the resulting compound into a leaving group by the conventional method. For example, the conversion of the hydroxy group into trifluoromethanesulfonyloxy group can be carried out by

using triflic anhydride at 0°C in the presence of a base(e.g., pyridine, NEt_3, DIEA) in an organic solvent (e.g., CH_2Cl_2, THF or a mixture thereof).

The compound [III] may be prepared by:
(1) condensing the compound of the formula [VIa]:



[VIa]

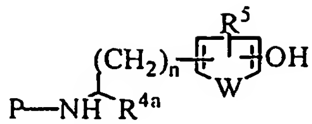
wherein P is a protecting group for an amino group and other symbols are the same as defined above with the compound [V] by a conventional aryl coupling method which is well known as Suzuki coupling method,
(2) removing the protecting group for the amino group of the resulting compound.

The protecting group for the amino group can be selected from a conventional protecting group for an amino group, for example, a substituted or unsubstituted aryl-lower alkoxycarbonyl group (e.g., benzyloxycarbonyl group, p-nitrobenzyloxycarbonyl group), a lower alkoxycarbonyl group (e.g., tert-butoxycarbonyl group) and the like.

The removal of the protecting group for the amino group can be carried out by a conventional method, which is selected according to the type of the protecting group to be removed, for example, catalytic reduction using a catalyst (e.g., palladium on activated carbon), treatment with an acid (e.g., TFA) and the like.

The condensation reaction can be carried out in a similar manner as described for the coupling reaction of the compound [IV] and [V].

The compound [VIa] wherein X^1 is trifluoromethanesulfonyloxy group may be prepared by reacting the compound of the formula [VIb]:



[VIb]

wherein the symbols are the same as defined above with triflic anhydride in a similar manner as described for the preparation of the compound [IV].

The compound [V] may be prepared by a conventional method (e.g., reference (a) Kuivila et al., J. Am. Chem. Soc., **1961**, *83*, 2159; (b) Gerrard, The Chemistry of Boron; Academic Press: New York, 1961; (c) Muetterties, The Chemistry of Boron and its Compounds: Wiley: New York, 1967; (d) Alamansa et al., J. Am. Chem. Soc., **1994**, *116*, 11723-11736):

(1) reacting a substituted or unsubstituted aryl lithium or a substituted or unsubstituted heteroaryl lithium with trimethyl borate at a temperature of -100°C to room temperature in an organic solvent (e.g., diethyl ether, THF or the mixture thereof), and

(2) hydrolyzing the resulting compound by a conventional method.

The hydrolysis can be carried out at room temperature in an organic solvent (e.g., diethyl ether, THF or the mixture thereof) in the presence of mild acid (e.g., AcOH or citric acid) and water.

The desired compound [I] of the present invention can be converted to each other. Such conversion of the present compound [I] into the other compound [I] may be carried out in an organic solvent by selecting one of the following procedures (Procedure A to K) according to the type of the substituent thereof. The organic solvent can be selected from any one which does not disturb the said procedure.

Procedure A: Reduction of Carbonyl Group

The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a hydroxy-lower alkyl group such as a hydroxymethyl group or a group of the formula: lower alkyl-CH(OH)- can be prepared by the reduction of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a carboxyl group, a formyl group or a group of the formula: lower alkyl-CO-. The reduction reaction can be carried out by a conventional method using a reducing agent such as borane, alkali metal borohydride (e.g., sodium borohydride) and the like at a temperature of 0°C to room temperature in an organic solvent, e.g., methanol, ethanol, THF or the mixture thereof.

Procedure B: Oxidation of Formyl Group

The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a carboxyl group can be prepared by the oxidation of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a formyl group. The oxidation reaction can be carried out by a conventional method using an oxidizing agent, e.g., $KMnO_4$ and the like at a temperature of 0°C to 50°C, preferably at a temperature of 30°C to 50°C, in an organic solvent, e.g., acetone, H_2O or the mixture thereof.

Procedure C: Reduction of Nitro Group

The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is an amino group or has an amino group can be prepared by the reduction of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a nitro group or has a nitro group. The reduction reaction can be carried out by a conventional method, e.g., 1) a catalytic reduction using a

catalyst such as Raney-nickel or a palladium on activated carbon and the like under a hydrogen atmosphere at room temperature in an organic solvent, e.g., methanol, H_2O or the mixture thereof, 2) chemical reduction using metal and inorganic acid, such as Fe/HCl, Sn/HCl, $SnCl_2$/HCl and the like, or 3) reduction with a reducing agent, such as $Na_2S_2O_4$, in a suitable solvent, e.g., methanol, ethanol, H_2O or the mixture thereof or without a solvent at a temperature of 0 °C to 80 °C.

Procedure D: Removal of Protecting Group

(D-1) The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is an amino group or has an amino group can be prepared by the deprotection of the amino group of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 groups is an N-protected amino group or has an N-protected amino group and the protecting group is a conventional protecting group for an amino group, e.g., benzyloxycarbonyl group, tert-butoxycarbonyl group, 9-fluorenylmethoxycarbonyl group, allyl group and the like. The deprotection reaction can be carried out by a conventional method, which is selected according to the type of the protecting group to be removed, e.g., 1) catalytic reduction using a catalyst such as palladium on activated carbon under a hydrogen atmosphere, 2) a treatment with an acid such as hydrogen chloride or TFA, 3) a treatment with an amine such as piperidine, 4) a treatment with a catalyst such as Wilkinson's catalyst, at room temperature or with heating in an organic solvent, e.g., CH_2Cl_2, THF, MeOH, EtOH and MeCN, or without an organic solvent.

(D-2) The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a sulfamoyl group can be prepared by the deprotection of the compound [I] wherein

the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is an N-protected sulfamoyl group and the protecting group is a conventional protecting group for a sulfamoyl group, e.g., tert-butyl group and the like. The deprotection reaction can be carried out by a conventional method, which is selected according to the type of the protecting group to be removed, e.g., a treatment with an acid such as TFA at a room temperature in an organic solvent, e.g., CH_2Cl_2 , or without an organic solvent.

(D-3) The compound [I] wherein R^1, R^2, R^3, R^4, R^5 or the substituent of the R^6 group is a carboxyl group or has a carboxyl group can be prepared by the deprotection of the compound [I] wherein the corresponding R^1, R^2, R^3, R^4, R^5 or the substituent of the R^6 group is a protected carboxyl group or has a protected carboxyl group and the protecting group is a conventional protecting group for a carboxyl group, e.g., a lower alkyl group, a lower alkenyl group, a lower alkynyl group, an aryl-lower alkyl group, an aryl group and the like. The deprotection reaction can be carried out by a conventional method, which is selected according to the type of the protecting group to be removed, for example, hydrolysis using a base (e.g., NaOH, LiOH, KOH) or an acid (e.g., hydrochloric acid) treatment with an acid (e.g., TFA), catalytic reduction using a catalyst (e.g., palladium on activated carbon) and the like, at room temperature in an organic solvent (e.g., MeOH, EtOH or THF) or without an organic solvent.

(D-4) The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a hydroxyl group or has a hydroxyl group can be prepared by the deprotection of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a protected hydroxyl group or has a protected hydroxyl group and the protecting group

is a conventional protecting group for a hydroxyl group, e.g., a methyl group, methoxymethyl group, tetrahydropyranyl group and the like. The deprotection reaction can be carried out by a conventional method, which is selected according to the type of the protecting group to be removed, for example, a treatment with BBr_3 for the demethylation of a methoxy group, and a treatment with HCl at a temperature of -78 °C to room temperature in an organic solvent, e.g., CH_2Cl_2 and MeOH for removal of methoxymethyl group.

Procedure E: Acylation of Amino Group

(E-1) The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is an N-acylamino group, e.g., a lower alkanoylamino group, a lower alkoxycarbonylamino group, an arylcarbonylamino group, a chlorosulfonylcarbamoylamino group (such as 3-chlorosulfonylureido group), a lower alkyl carbamoylamino group (such as 3-(lower alkyl) ureido group), a substituted or unsubstituted arylcarbamoyl amino group (such as 3-(substituted or unsubstituted aryl) ureido group), a (substituted or unsubstituted lower alkyl)thiocarbamoylamino group (such as 3-(lower alkyl)thioureido group, 3-(phenyl-lower alkyl)thioureido group) can be prepared by the N-acylation of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is an amino group. The N-acylation reaction can be carried out by a conventional method using 1) an acylating reagent, e.g., a lower alkanoyl halide, a lower alkanoic acid anhydride, a lower alkyl halogenoformate such as a lower alkyl chloroformate, an aryl carbonyl halide, a chlorosulfonyl isocyanate, a lower alkyl isocyanate, a substituted or unsubstituted aryl isocyanate or a lower alkyl isocyanate, or 2) when preparing a lower alkoxycarbonylamino group, a (lower

alkyl)carbamoylamino group, a substituted or unsubstituted arylcarbamoyl amino group, a (substituted or unsubstituted lower alkyl)thiocarbamoylamino group, a condensing reagent, e.g., CDI, thioCDI, and a requisite amine or alcohol, at a temperature of 0 °C to 100 °C, preferably at a temperature of room temperature to 90 °C, with a base (e.g., DIEA, DMAP, pyridine, $NaHCO_3$, Na_2CO_3, $KHCO_3$, K_2CO_3) or without a base in an organic solvent (e.g., THF, CH_3CN, CH_2Cl_2, DMF, toluene, acetone and the mixture thereof).

(E-2) The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is an N-(lower alkylsulfonyl) amino group (e.g., methanesulfonylamino group), an N-(substituted or unsubstituted arylsulfonyl)amino group (e.g., p-toluenesulfonylamino group, benzenesulfonylamino group) or an N-(substituted or unsubstituted heteroarylsulfonyl)amino group (e.g., quinolinosulfonylamino group) can be prepared by the N-sulfonylation of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is an amino group. The N-sulfonylation reaction can be carried out by a conventional method using a lower alkylsulfonyl halide or a substituted or unsubstituted arylsulfonyl halide or a substituted or unsubstituted heteroarylsulfonyl halide in the presence of a base (e.g., pyridine, DMAP, Et_3N, DIEA, $NaHCO_3$, $KHCO_3$, Na_2CO_3, K_2CO_3) at a temperature of 0°C to room temperature, preferably at room temperature, in an organic solvent (e.g., CH_2Cl_2, THF, DMF, CH_3CN, toluene, acetone and the mixture thereof).

(E-3) The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a ureido group can be prepared by the hydrolysis of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6

group is a 3-chlorosulfonylureido group. The hydrolysis can be carried out using a base (e.g., LiOH, NaOH and the like) or an acid (e.g., HCl) at room temperature in a suitable solvent (e.g., THF, CH_3CN, H_2O) or a mixture thereof.

Procedure F: Alkylation of Hydroxyl Group

The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a substituted or unsubstituted lower alkoxy group, e.g., a substituted or unsubstituted hetero-cycloalkyl-lower alkoxy group (such as a substituted or unsubstituted piperidyl-lower alkoxy group, or a substituted or unsubstituted pyrrolidinyl-lower alkoxy group), an aryl-lower alkoxy group, a heteroaryl-lower alkoxy group (such as a pyridyl-lower alkoxy group, a substituted or unsubstituted thiazolyl-lower alkoxy group, a substituted or unsubstituted isoxazolyl-lower alkoxy group, a substituted or unsubstituted thienyl-lower alkoxy group), a lower alkoxycarbonyl-lower alkoxy group, a carboxy-lower alkoxy group, a hydroxy-lower alkoxy group, a cyano-lower alkoxy group or a lower alkoxy group, can be prepared by the alkylation of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a hydroxy group, followed by the deprotection of the protecting group for carboxyl group or hydroxyl group by a conventional method, if desired. The alkylation reaction can be carried out using a halogenated lower alkane not having a substituent (e.g., methyl iodide) or that having a substituent such as a substituted or unsubstituted aryl group (e.g., unsubstituted aryl-lower alkyl halide such as benzyl bromide), a substituted or unsubstituted heteroaryl group (e.g., substituted or unsubstituted heteroaryl-lower alkyl halide such as pyridylmethyl bromide, isoxazolylmethyl bromide, thiazolylmethyl bromide), a heterocycloalkyl group (e.g., substituted heterocycloalkyl-lower alkyl halide such as N-

lower alkylpyrrolidinyl-lower alkyl bromide, N-lower alkylpiperidyl-lower alkyl bromide), a lower alkoxycarbonyl group (e.g., halogenoalkanoic acid lower alkyl ester such as methyl bromoacetate) or a cyano group (e.g., bromoacetonitrile) in the presence of a base (e.g., Et_3N, DIEA, $NaHCO_3$, $KHCO_3$, Na_2CO_3, K_2CO_3, $KHCO_3$, $CsCO_3$) at a temperature of room temperature to 50°C in an organic solvent (e.g., CH_2Cl_2, THF, DMF, CH_3CN, toluene).

The alkylation reaction can be also carried out by using a conventional alkylation method such as Mitsunobu Reaction (for reference of Mitsunobu reaction: (a) Mitsunobu, *Synthesis,* 1-28, (1981), (b) Hughes, *Organic Reactions*, 42, 335 (1992), (c) Mitsuhashi et al., *J. Am. Chem. Soc.*, 94, 26 (1972)).

Procedure G: Halogenation of Hydroxyl Group

The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a halogenated lower alkyl group can be prepared by the halogenation of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a hydroxyl lower alkyl group. The halogenation reaction can be carried out by the conventional method using, for example, a combination of tetrahalomethane (e.g., CBr_4) and triphenylphosphine at a room temperature in an organic solvent (e.g., CH_2Cl_2).

Procedure H: Conversion of Halogenated Alkyl Group to Alkoxy Alkyl Group

The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a lower alkoxy-lower alkyl group can be prepared by reacting the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a halogenated lower alkyl group with an alkali

metal lower alkoxide (e.g., sodium methoxide) at room temperature in an organic solvent (e.g., DMF, THF, CH_3CN).

Procedure I: Conversion of Carboxyl Group into Carbamoyl Group

The compound [I] wherein R^1, R^2, R^3, R^4, R^5 or the substituent of the R^6 group is a substituted or unsubstituted carbamoyl group (e.g., an N-lower alkylcarbamoyl group, an N,N-(lower alkyl)(lower alkyl) carbamoyl group, an N-(hydroxy-lower alkyl)carbamoyl group, an N-(morpholino-lower alkyl)carbamoyl group, an N-(aryl-lower alkyl)carbamoyl group, an N-(lower alkanesulfonyl)carbamoyl group, a hydroxycarbamoyl group, a carbamoyl group) can be prepared by condensing the compound [I] wherein the corresponding R^1, R^2, R^3, R^4, R^5 or the substituent of the R^6 group is a carboxyl group with a substituted or unsubstituted amine (e.g., a lower alkylamine, an N,N-(lower alkyl)(lower alkyl)amine, a (hydroxy-lower alkyl)amine, a (morpholino-lower alkyl)amine, an (aryl-lower alkyl)amine, hydroxyamine, ammonia) or a lower alkanesulfonamide.

The condensation reaction can be carried out by the conventional method for a usual peptide synthesis as described for the condensing reaction of the compound [II] and [III].

Procedure J: Reductive Alkylation

(J-1) The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is an amino-lower alkyl group, a lower alkyl amino-lower alkyl group or an arylamino-lower alkyl group can be prepared by the reductive alkylation of the corresponding ammonia, lower alkyl amine or aryl amine with the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a formyl group. The reductive alkylation reaction

can be carried out by the conventional method using a reductive agent (e.g., sodium cyanoborohydride) and an acid (e.g., HCl) at room temperature in an organic solvent (e.g., MeOH, THF, dioxane, or the mixture thereof).

(J-2) The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is an N,N-dimethylamino group can be prepared by the reductive alkylation of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is an amino group. The reductive alkylation can be carried out by the conventional method using formaldehyde, a reducing agent (e.g., sodium cyanoborohydride) and an acid (e.g., HCl) at room temperature in an organic solvent (e.g., MeOH, EtOH, THF, dioxane) or H_2O , or the mixture thereof.

Procedure K: Wittig Reaction

The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a lower alkokycarbonyl-ethenyl group can be prepared by the Wittig reaction of the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a formyl group. The Wittig reaction can be carried out by the conventional method using, for example, (triphenylphosphoranylidene)-acetic acid lower alkyl ester at a temperature of 50°C to 100°C in an organic solvent (e.g., toluene, THF).

Procedure L: Conversion of Halogenated Alkyl group to Amino Alkyl group

The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a lower alkyl group which is substituted by a substituted or unsubstituted amino group, a substituted or unsubstituted piperidinyl group, a substituted or unsubstituted morpholino group, a

thiomorpholino group which may be oxidized, a substituted or unsubstituted piperazinyl group, or a substituted or unsubstituted pyrrolidinyl group can be prepared by reacting the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a halogenated lower alkyl group with a requisite amine at room temperature or under cooling in an organic solvent (e.g., DMF, THF, CH_2Cl_2) or without a solvent, with or without a base such as Et_3N, DIEA.

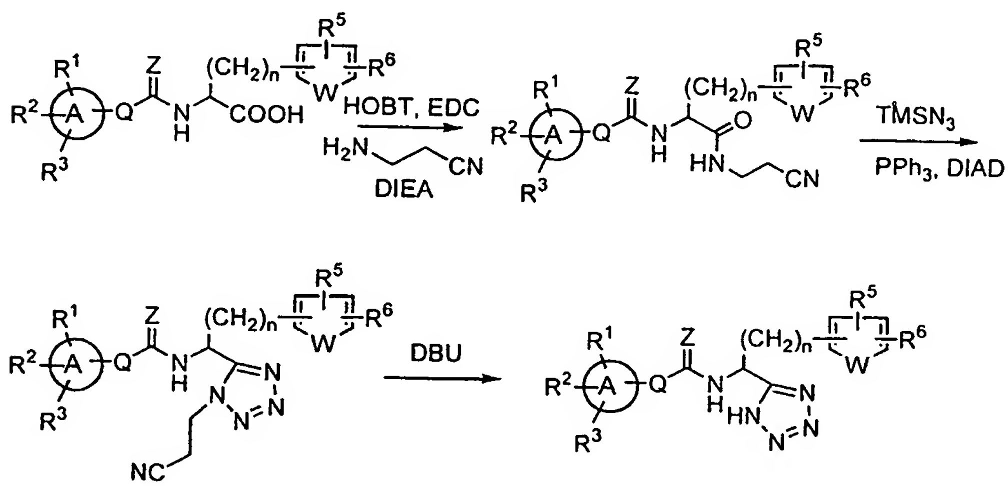
In particular, the compound [I] wherein R^1 and R^5 are hydrogen atoms, R^2 and R^3 are halogen atoms, and R^6 is a phenyl group substituted by a lower alkoxy group and a lower alkyl group which is substituted by a group selected from the group consisting of a substituted or unsubstituted amino group, a substituted or unsubstituted piperidinyl group, a substituted or unsubstituted morpholino group, a substituted or unsubstituted piperazinyl group and a substituted or unsubstituted pyrrolidinyl group can be prepared by reacting the compound [I] wherein R^1 and R^5 are hydrogen atoms, R^2 and R^3 are halogen atoms, and R^6 is a phenyl group substituted by a lower alkoxy group and a halogeno-lower alkyl group with a requisite amine such as a substituted or unsubstituted ammonia, a substituted or unsubstituted piperidine, a substituted or unsubstituted morpholine, a substituted or unsubstituted piperazine and a substituted or unsubstituted pyrrolidine. The reaction can be carried out as described above.

Procedure M: Conversion of Carbonyl group to Thiocarbonyl group

The compound wherein Z is sulfur atom can be prepared by reacting the compound [I] wherein Z is oxygen atom with Lawesson's reagent in a suitable organic solvent (e.g., toluene, xylene) at a temperature of 50 °C to 150 °C.

Procedure N: Conversion of Carboxyl group to Tetrazolyl group

The compound [I] wherein R_4 is tetrazolyl group can be prepared from the compound [I] wherein R_4 is carboxyl group following the procedure described in the J. Med. Chem., 41, 1513-1518, 1998. The procedure can be summarized in the following scheme:



Procedure O: Conversion of Carboxyl group to Alkoxycarbonyl group

The compound [I] wherein R^1, R^2, R^3, R^4, R^5 or the substituent of the R^6 group is a substituted or unsubstituted lower alkoxycarbonyl group can be prepared by condensing the compound [I] wherein the corresponding R^1, R^2, R^3, R^4, R^5 or the substituent of the R^6 group is a carboxyl group with a substituted or unsubstituted alcohol (e.g., a halogeno-lower alcohol, pyridyl-lower alcohol, a (lower alkylamino)-lower alcohol, a lower alkoxy-lower alcohol).

The condensation reaction can be carried out by the conventional method for a usual ester synthesis as described for Method A-(3).

Procedure P: Reduction of Hydroxyl group

The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a lower alkyl group can be prepared by reducing the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a hydroxy-lower alkyl group. The reduction can be carried out using a reducing reagent such as a silane compound (e.g., Et_3SiH) in the presence of Lewis acid (e.g., BF_3, $TiCl_4$) in a suitable organic solvent (e.g., MeCN, CH_2Cl_2, THF) at a temperature of 0 °C to -78 °C.

Procedure Q: Halogenation of phenyl group

The compound [I] wherein R^6 is a substituted or unsubstituted halogeno-phenyl group can be prepared by reacting the compound [I] wherein R^6 is a substituted or unsubstituted phenyl group with halogenating reagent (e.g., Bu_4NBr_3, 3,5-dichloro-1-fluoropyridinium triflate) in a suitable solvent (e.g., MeCN, CH_2Cl_2, THF) at room temperature or with heating.

Procedure R: Nitration of phenyl group

The compound [I] wherein R^6 is a substituted or unsubstituted nitro-phenyl group can be prepared by reacting the compound [I] wherein R^6 is a substituted or unsubstituted phenyl group with HNO_3 in a suitable solvent (e.g., THF, NeCN, MeOH, EtOH) at a temperature of room temperature to 100 °C.

Procedure S: Converting phenyl group to carbamoyl-phenyl group

The compound [I] wherein R^6 is a substituted or unsubstituted carbamoyl-phenyl group can be prepared by 1) reacting the compound [I] wherein R^6 is a substituted or unsubstituted phenyl group with chlorosulfonyl isocyanate

and 2) hydrolyzing the obtained compound. The reaction of the compound [I] and the isocyanate can be carried out in a suitable solvent (e.g., MeCN, CH_2Cl_2, THF) at a temperature of 0 °C to room temperature. The hydrolysis can be carried out with an acid (e.g., HCl, HNO_3, H_2SO_4) in a suitable solvent (e.g., MeCN, H_2O) at a temperature of room temperature to 100 °C.

Procedure T: Conversion of Alkanoyl group to imino-alkyl group

The compound [I] wherein R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a (hydroxyimino)-lower alkyl or (a lower alkoxyimino)-lower alkyl group can be prepared by reacting the compound [I] wherein the corresponding R^1, R^2, R^3, R^5 or the substituent of the R^6 group is a lower alkanoyl group with hydroxyamine or a lower alkoxyamine in a suitable solvent such as a lower alcohol (e.g., MeOH, EtOH, PrOH or BuOH) and MeCN, with a base such as alkali metal acetate (e.g., NaOAc) at room temperature or with heating.

Procedure U: Conversion of halogen atom to heterocyclic group

The compound [I] wherein R^1, R^2 or R^3 is a substituted or unsubstituted heterocyclic group can be prepared by reacting the compound [I] wherein the corresponding R^1, R^2 or R^3 is halogen atom with a (substituted or unsubstituted heterocyclic)boronic acid using a conventional aryl coupling method such as Suzuki Coupling method. The coupling reaction can be carried out following the procedure as describe in Method A.

Procedure V: Oxidation of Sulfur Atom

The compound [I] wherein the substituent of the R^6 group is a lower alkylsulfinyl group, a lower alkylsulfonyl group, a thiomorpholino-lower alkyl S-oxide group a thiomorpholino-lower alkyl S,S-dioxide group can be prepared by oxidizing the compound [I] wherein the corresponding substituent of the R^6 group is a lower alkylthio group or a thiomorpholino-lower alkyl group with an oxidant such as a peracid (e.g., mCPBA, H_2O_2, AcOOH, PhCOOOH) in a suitable solvent (e.g., CH_2Cl_2) at room temperature or under cooling.

Procedure W: Imidation of hydroxy-lower alkyl

The compound [I] wherein R^1, R^2, R^3 or the substituent of the R^6 group is a lower alkyl group which is substituted by succinimido group or 2,5-dioxo-1-imidazolidinyl group optionally substituted by a lower alkyl group can be prepared by the imidation of the compound [I] wherein the corresponding R^1, R^2, R^3 or the substituent of the R^6 group is a hydroxy-lower alkyl group. The imidation can be carried out by using a conventional method such as Mitsunobu Reaction (reference of Mitsunobu reaction is made in Procedure F). The reaction can be carried out by reacting the compound [I] with a di(lower alkyl) azodicarboxylate (e.g., diethyl azodicarboxylate), a tri(lower alkyl)- or triarylphosphine (e.g., triphenylphospphine), and a requisite imide (e.g., succinimide or hydantoin optionally substituted by a lower alkyl group), in a suitable organic solvent (e.g., Et_2O and THF) at a temperature of -20°C to 50°C.

The active ingredient of the present invention are exemplified by the following examples but not limited thereby.

Examples

Example 1: N-(2,6-Dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (1A) and N-(2,6-Dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine (1B).

1) Pyridine (3.58 mL) was added to a solution of N-(*tert*- butoxycarbonyl)-L-tyrosine methyl ester (4.36 g) in anhydrous CH_2Cl_2 (100 mL) under N_2. The solution was cooled to 0 ^{0}C and triflic anhydride (3 mL) was added dropwise with stirring. After the addition was over the ice-bath was removed and the mixture was stirred for 3 h at room temperature. The mixture was sequentially washed with water, 1 N HCl and water. The resulting CH_2Cl_2 solution was finally washed with $NaHCO_3$, followed by water, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: toluene/EtOAc 9:1) to yield N-(*tert*-butoxycarbonyl)-O-(trifluoromethanesulfonyl)-L-tyrosine methyl ester (6.2 g). ESMS: m/z 500 (MH^+).

2) To a mixture of 2-methoxybenzene boronic acid (0.446 g) and anhydrous K_2CO_3 (0.84 g) in toluene/DMF (25 mL/2.5 mL) under N_2 was added a solution of the product obtained above (1.0 g) in 5 mL of toluene. $Pd(PPh_3)_4$ (0.48 g) was added and the mixture was heated at 80 ^{0}C for 24 h. The mixture was cooled, filtered through Celite and evaporated. The residue was taken up in EtOAc and washed with water. The organic layer was dried ($MgSO_4$), evaporated, and the crude material was purified by flash column chromatography (silica gel; eluent: EtOAc/hexane 1/3) to yield N-(*tert*-butoxycarbonyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (0.64 g). ESMS: m/z 386 (MH^+).

3) To a solution of the product obtained above (2.97 g) in CH_2Cl_2 (20 mL) was added TFA (20 mL) and the mixture

stirred for 1.5 h. The solution was evaporated. The residue was dissolved in CH_2Cl_2 (20 mL) and the solution was evaporated. This process was repeated once more and finally the residue was dried under high vacuum to yield the TFA salt of 4-(2-methoxyphenyl)-L-phenylalanine methyl ester (2.93 g). ESMS: m/z 286 (MH^+).

4) To a solution of the product obtained above (2.3 g) in CH_2Cl_2 (30 mL) containing DIEA (2.24 g) at 0 ^{0}C was added a solution of 2,6-dichlorobenzoyl chloride (0.99 mL) with stirring. The mixture was warmed to room temperature and stirred for 24 h. The mixture was washed sequentially with water, 1N HCl, satd. $NaHCO_3$ and brine. The resulting CH_2Cl_2 solution was dried ($MgSO_4$), evaporated, and the crude material was purified by flash column chromatography (silica gel; eluent: EtOAc/hexane 1/4) to yield N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (1.64 g) (1A). ESMS: m/z 458 (MH^+).

5) The product obtained above (0.1 g) was dissolved in a mixture of THF/ MeOH (5 mL/ 2 mL). A solution of LiOH (monohydrate, 14 mg) in 2 mL of water was added and the mixture was stirred at room temperature for 3 h. The mixture was evaporated and the residue was treated with water. The resulting mixture was adjusted to pH 2 with 1N HCl and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and evaporated to N-(2,6-Dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine (0.08 g) (1B). ESMS: m/z 444 (MH^+). mp. 211 °C.

Example 2: N-[(S)-2-Phenylpropionyl]-4-(2-methoxyphenyl)-L-phenylalanine.

1) A mixture of 4-(2-methoxyphenyl)-L-phenylalanine methyl ester hydrochloride (0.03 g), (S)-2-phenylpropionic acid (0.014 g), EDC (0.02 g), HOBT (0.021 g) and DIEA (0.034 mL) in DMF (5 mL) was stirred at room temperature for 18 h. DMF was removed and the residue was partitioned

between EtOAc and water. The organic layer was evaporated and washed sequentially with 10% citric acid, satd. $NaHCO_3$ and brine. The resulting organic layer was dried ($MgSO_4$), evaporated and the residue was purified by flash column chromatography (silica gel; eluent: CH_2Cl_2/EtOAc 9:1) to yield N-[(S)-2-phenylpropionyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (0.031g). ESMS: m/z 417 (MH^+).

2) The product obtained above (0.031 g) was dissolved in a mixture of THF/MeOH (3 mL/0.3 mL). 2N LiOH (0.07 mL) was added and the mixture was stirred at room temperature for 3h. The mixture was evaporated and the residue was treated with water. The resulting mixture was adjusted to pH 2 with 1N HCl and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried and evaporated to yield the title compound (0.02 g). ESMS: m/z 403 (MH^+).

Example 3: N-(2,6-Difluorobenzoyl)-4-(2, 6-dimethoxyphenyl)-L-phenylalanine.

1) 2,6-Dimethoxybenzeneboronic acid (0.5 g) was dissolved in DME (10 mL). To the solution was added K_2CO_3 (0.7 g), N-(*tert*-butoxycarbonyl)-O-(trifluoromethane-sulfonyl)-L-tyrosine methyl ester (0.4 g), $Pd(Ph_3P)_4$ (0.6 g) and water (0.2 mL). The resulting mixture was heated to 80 °C overnight. Subsequently EtOAc and water were added to the mixture. The EtOAc layer was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: EtOAc/hexane 1:2) to give N-(tert-butoxycarbonyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (380 mg).

2) To the product obtained above was added CF_3COOH (5 mL) and the mixture was stirred at room temperature for 4 h. The excess CF_3COOH was removed under reduced pressure.

The residue was dissolved in CH_2Cl_2 and washed with saturated sodium bicarbonate. The organic phase was dried ($MgSO_4$) and evaporated to give 4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (260 mg).

3) The product obtained above (140 mg) was dissolved in dry CH_2Cl_2 (10 mL). To the mixture was added Et_3N (0.15 mL) and 2,6-difluorobenzoyl chloride (72 μL) and the mixture was stirred at room temperature for 6 h. CH_2Cl_2 was added, and the organic phase was washed with water, dried ($MgSO_4$), and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: EtOAc/hexane 1:2) to give N-(2,6-difluorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester(160 mg). ESMS: m/z 455 (MH^+).

4) A solution of LiOH (monohydrate, 12 mg) in 0.4 mL of water was added to a solution of the product obtained above (90 mg) in THF (5 mL). Few drops of MeOH were added and the mixture was stirred at room temperature overnight. The excess organic solvent was removed under reduced pressure, water was added to the residue and the resulting solution was acidified with 10 % citric acid. The resulting solid was collected by filtration, washed with water and dried to give the title compound (70 mg). ESMS: m/z 441 (MH^+).

Example 4: N-(2,6-Dichlorobenzoyl)-4-(2-thienyl)-L-phenylalanine methyl ester (4A) and : N-(2,6-Dichlorobenzoyl)-4-(2-thienyl)-L-phenylalanine (4B).

1) To a mixture of 2-thienylboronic acid (1.135 g) and anhydrous K_2CO_3 (2.23 g) in toluene/DMF (75 mL /7.5 mL) under N_2 was added a solution of N-(tert-butoxycarbonyl)-O-(trifluoromethanesulfonyl)-L-tyrosine methyl ester (3.42 g) in 5 mL of toluene. $Pd(PPh_3)_4$ (1.4 g) was added and the mixture was heated at 80 ^0C for 24 h. After usual work-up as shown in Example 1 the crude material was purified by

flash column chromatography (silica gel; eluent: EtOAc/hexane 1:3) to yield N-(tert-butoxycarbonyl)-4-(2-thienyl)-L-phenylalanine methyl ester(1.81 g). ESMS: m/z 362 (MH^+).

2) To a solution of the product obtained above (1.53 g) in CH_2Cl_2 (25 mL) was added TFA (25 mL) and the mixture was stirred for 1.5 h at room temperature. The mixture was evaporated. The residue was partitioned between CH_2Cl_2 (20 mL) and satd. $NaHCO_3$. The organic layer was separated, washed with brine, dried ($MgSO_4$) and evaporated to give 4-(2-thienyl)-L-phenylalanine methyl ester. The free base was treated with a solution of 10% HCl in Et_2O to provide the HCl salt (1.036 g). ESMS: m/z 262 (MH^+).

3) To a mixture of the HCl salt obtained above (0.2 g) in CH_2Cl_2 (5 mL) containing DIEA (0.42 mL) at 0 ^{0}C was added a solution of 2,6-dichlorobenzoyl chloride (0.12 mL) in CH_2Cl_2 (1 mL). The mixture was warmed to room temperature and stirred for 24 h, and washed sequentially with water, 1N HCl, saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), evaporated, and the residue was purified by flash column chromatography (silica gel; eluent: CH_2Cl_2/ EtOAc/hexane 1:1:6) to yield N-(2,6-dichlorobenzoyl)-4-(2-thienyl)-L-phenylalanine methyl ester (0.15 g) (4A). ESMS: m/z 434 (MH^+).

4) The product obtained above (0.1 g) was dissolved in a mixture of THF/ MeOH (5 mL/ 2 mL). A solution of LiOH (monohydrate, 14 mg) in 2 mL of water was added and the mixture was stirred at room temperature for 3 h. The mixture was evaporated and the residue was treated with water. The mixture was adjusted to pH 2 with 1N HCl and extracted with EtOAc. The extract was washed with brine, dried ($MgSO_4$) and evaporated to yield : N-(2,6-Dichlorobenzoyl)-4-(2-thienyl)-L-phenylalanine (0.08 g) (4B). ESMS: m/z 420 (MH^+).

Example 5: N-(2,6-Dichlorobenzoyl)-4-(2-methoxyphenyl) -D-phenylalanine.

1) A solution of 2,6-dichlorobenzoylchloride (0.68 mL) in CH_2Cl_2 (5 mL) was added to a solution of an ice-cold solution of D-tyrosine methyl ester HCl salt (1.0 g) and DIEA (2.26 mL) in CH_2Cl_2 (15 mL). The mixture was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (50 mL) and washed successively with H_2O, 1 N HCl and brine. The organic layer was dried ($MgSO_4$) and evaporated, and the residue was recrystallized from EtOAc and hexanes to yield 1.46 g of N-(2,6-dichlorobenzoyl)-D-tyrosine methyl ester. ESMS: m/z 369 (MH^+).

2) Triflic anhydride (0.27 mL) was added slowly to an ice-cold solution of the product obtained above (0.5 g) in CH_2Cl_2 containing pyridine (0.33 mL). The mixture was stirred for 2.5 h and was washed successively with water, 1 N HCl, satd. $NaHCO_3$ and water. The organic layer was dried ($MgSO_4$), evaporated and the residue was purified by flash column chromatography (silica gel; eluent: toluene/EtOAc 9:1) to yield 0.65 g of N-(2,6-dichlorobenzoyl)-O-(trifluoromethanesulfonyl)-D-tyrosine methyl ester. ESMS: m/z 501 (MH^+).

3) $Pd(PPh_3)_4$ (0.09 g) was added to a suspension of 2-methoxybenzene boronic acid (0.082 g), K_2CO_3 (0.16 g) and the product obtained above (0.214 g) in toluene/DMF (4 mL/0.4 mL) under N_2. The mixture was heated at 80 °C for 24 h, cooled, filtered and the solvent was evaporated. The residue was taken up with EtOAc, washed with water, dried ($MgSO_4$) and evaporated. The crude product was purified by flash column chromatography (silica gel; eluent: toluene/EtOAc 10:1) to yield 45 mg of N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)- D-phenylalanine methyl ester. ESMS: m/z 458 (MH^+).

4) The product obtained above (90 mg) was hydrolyzed with LiOH in a similar manner as described for the

preparation of Example 1 to give 25 mg of the title compound. ESMS: m/z 444 (MH^+). mp. 195 °C.

Example 6: N-(2,6-Dichlorobenzoyl)-3-(2-methoxyphenyl)-DL-phenylalanine.

By following the same procedure as Example 5, the title compound was obtained. ESMS: m/z 444 (MH^+). mp. 104 °C.

Example 7: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (7A) and N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine (7B).

1) 1,3-Dimethoxybenzene (4 g) was dissolved in freshly distilled THF (10 mL). This solution was cooled to -78 °C and n-BuLi (24 mL, 1.6 M solution in hexanes) was added dropwise to the cold solution. The mixture was stirred at -78 °C for 1 h, then warmed to room temperature and stirred for 1 h. The resulting mixture was cooled again to -78 °C and $(MeO)_3B$ (6.7 mL) was added. The mixture was allowed to warm to room temperature and stirred overnight. Water (10 mL) was added, and the mixture was stirred for 0.5 h, acidified to pH 4 with acetic acid and extracted with EtOAc. The extract was dried ($MgSO_4$) and evaporated to give 2,6-dimethoxybenzeneboronic acid, which was used without further purification.

2) The product obtained above (0.3 g) and K_2CO_3 (0.5 g) were suspended in DME (10 mL). To the mixture was added N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine methyl ester (0.3 g), $Pd(Ph_3P)_4$ (0.3 g), water (0.4 mL) and the mixture was heated at 80 °C for 6 h. After cooling, EtOAc and water were added to the mixture. The EtOAc phase was dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (silica gel; eluent:

EtOAc/hexanes 1:2) to give 0.2 g of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (7A).

3) The product obtained above (0.1 g) was dissolved in dry THF (5 mL). To the solution was added a solution of LiOH (monohydrate, 12 mg) in 0.5 mL of water and a few drops of MeOH. The mixture was stirred at room temperature for 2 h, and evaporated. The residue was dissolved in water and acidified with 10% citric acid. The separated solid was collected by filtration and dried to give 80 mg of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxyphenyl)-L-phenylalanine. ^{1}H NMR (300MHz. DMSO-d_6): δ 2.9 (dd, 1H), 3.2 (dd, 1H) , 3.7 (s, 6H), 4.72 (m, 1H), 6.7 (d, 2H), 7.1-7.5 (m, 8H), 9.1 (d, 1H). ESMS: m/z 474 (MH^+) 472 ($[M-H]^-$).

Example 8: N-(2,6-Dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine

1) HCl gas was bubbled into an ethanol (35 mL) solution of N-(tert-butoxycarbonyl)-4-bromo-L-phenylalanine (5 g) and the mixture was left overnight at room temperature. The separated solid was collected by filtration, washed with ether and air-dried to give 3.46 g of the HCl salt of 4-bromo-L-phenylalanine ethyl ester. ESMS: m/z 274 (MH^+).

2) DIEA (6.1 mL) was added to a suspension of the HCl salt obtained above (3.2 g) in CH_2Cl_2 (40 mL) at 0 °C. To the mixture was added a solution of 2,6-dichlorobenzoyl chloride (2.0 mL) in CH_2Cl_2 (5 mL) and the mixture was stirred overnight at room temperature. The solvent was removed and the residue was partitioned between 1N HCl and EtOAc. The organic layer was separated, washed with brine and evaporated. The product was purified by flash column chromatography (silica gel; eluent: hexanes/ EtOAc 4:1) to

yield 3.9 g of N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester. ESMS: m/z 446 (MH^+).

3) $Pd(PPh_3)_4$ (1.61 g) was added to a suspension of 2-methoxybenzene boronic acid (1.5 g), K_2CO_3 (2.83 g) and the product obtained above (3.65 g) in DME (50 mL) under Ar. The mixture was heated at 80 °C for 24 h, cooled, filtered and the solvent was evaporated. The residue was taken up in EtOAc and the EtOAc solution was washed with water, dried and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: hexanes/EtOAc 4:1) to yield 2.1 g of N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester. ESMS: m/z 472 (MH^+).

4) A solution of LiOH (monohydrate, 82 mg) in 1 mL of H_2O was added to a solution of the product obtained above (0.4 g) in THF/MeOH (5 mL /1 mL) and the mixture was stirred for 1.5 h. The solvent was removed and the residue was dissolved in water. The solution was acidified to pH 2 with 1N HCl and the separated solid was collected by filtration, washed with water and air-dried to give the title compound.

The following compounds (Example 9 to 14) were prepared by a procedure similar to the Example 7.

Example 9: N-(2,6-Dichlorobenzoyl)-4-(2,4-dimethoxyphenyl)-L-phenylalanine.
ESMS: m/z 474 (MH^+), 472 ($[M-H]^-$).

Example 10: N-(2,6-Dichlorobenzoyl)-4-(2,3,6-trimethoxyphenyl)-L-phenylalanine.
ESMS: m/z 504 (MH^+), 502 ($[M-H]^-$).

Example 11. N-(2,6-Dichlorobenzoyl)-4-(2,4,6-trimethoxyphenyl)-L-phenylalanine.

ESMS: m/z 504 (MH^+), 502 ($[M-H]^-$).

Example 12. N-(2,6-Dichlorobenzoyl)-4-(4-chloro-2,6-dimethoxyphenyl)-L-phenylalanine.
ESMS: m/z 509 (MH^+), 507 ($[M-H]^-$).

Example 13. N-(2,6-Dichlorobenzoyl)-4-(2,6-diethoxyphenyl)-L-phenylalanine.
ESMS: m/z 502 (MH^+), 500 ($[M-H]^-$).

Example 14. N-(2,6-Dichlorobenzoyl)-4-(2-ethoxy-6-methoxyphenyl)-L-phenylalanine.
ESMS: m/z 488 (MH^+), 486 ($[M-H]^-$).

Example 15. N-(2,6-Dichlorobenzoyl)-4-[2-[N-(tert-butyl)sulfamoyl]phenyl]-L-phenylalanine methyl ester.

2-[N-(tert-Butyl)sulfamoyl]benzeneboronic acid (0.4 g) was dissolved in DME (10 mL). To this solution was added K_2CO_3 (0.1 g), N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine methyl ester (0.1 g), $Pd(Ph_3P)_4$ (0.1 g) and water (0.2 mL). The mixture was heated at 80 °C overnight. After cooling, EtOAc and water were added to the mixture. The EtOAc phase was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: EtOAc/hexanes 1:2) to give 100 mg of the title compound. ESMS: m/z 585 ($[M+Na]^+$).

Example 16. N-(2,6-Dichlorobenzoyl)-4-[2-[N-(tert-butyl)sulfamoyl]phenyl]-L-phenylalanine.

N-(2,6-Dichlorobenzoyl)-4-[2-[N-(tert-butyl)sulfamoyl]phenyl]-L-phenylalanine methyl ester (75 mg) was dissolved in THF (5 mL) and to this solution was added a solution of LiOH (monohydrate, 10 mg) in water (0.4 mL). Few drops of MeOH were added and the mixture was stirred at room temperature overnight. The mixture was

evaporated, water was added to the residue and the mixture was acidified with 10% citric acid. The separated solid was collected by filtration, washed with water and dried to give 60 mg of the title compound. ESMS: m/z 549 (MH^+), 547 ($[M-H]^-$).

Example 17. N-(2,6-Dichlorobenzoyl)-4-(2-sulfamoylphenyl)-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-[2-[N-(tert-butyl)sulfamoyl]phenyl]-L-phenylalanine methyl ester (130 mg) was dissolved in TFA (2 mL), to this solution was added anisole (20 µM) and the mixture was stirred at room temperature for 6 h. TFA was removed under reduced pressure to give 100 mg of N-(2,6-dichlorobenzoyl)-4-(2-sulfamoylphenyl)-L-phenylalanine methyl ester. ESMS: m/z 507 (MH^+).

2) The product obtained above (100 mg) was hydrolyzed in a similar manner as described in Example 16 to give 80 mg of the title compound. ESMS: m/z 493 (MH^+), 491 ($[M-H]^-$).

Example 18. N-(2,6-Dichlorobenzoyl)-4-[2-(N-benzoylsulfamoyl)phenyl]-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-sulfamoylphenyl)-L-phenylalanine methyl ester (100 mg) was dissolved in anhydrous pyridine (5 mL). To this solution was added benzoyl chloride (50 µL) and the mixture was stirred for 12 h at room temperature under N_2. EtOAc and satd. $NaHCO_3$ were added to the mixture and the EtOAc phase was washed with 1 N HCl, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: EtOAc/hexanes 1:2) to give N-(2,6-dichlorobenzoyl)-4-[2-(N-benzoylsulfamoyl)phenyl]-L-phenylalanine methyl ester.

2) The product obtained above was hydrolyzed in a similar manner as described in Example 16 to give 80 mg of the title compound. ESMS: m/z 595 ([M-H]$^-$)

Example 19. N-(2,6-Dichlorobenzoyl)-4-[2-(N-acetylsulfamoyl) phenyl]-L-phenylalanine.

The title compound was prepared by a procedure similar to Example 18 by replacing benzoyl chloride with AcCl. ESMS: m/z 533 ([M-H]$^-$).

The following compounds (Examples 20 and 21) were prepared by a similar procedure and deprotection method as outlined in Examples 15 and 16, respectively.

Example 20. N-(2,6-Dichlorobenzoyl)-4-[2-(N-methylsulfamoyl)phenyl]-L-phenylalanine.
ESMS: m/z 505 ([M-H]$^-$).

Example 21. N-(2,6-Dichlorobenzoyl)-4-[2-(N,N-dimethylsulfamoyl)phenyl]-L-phenylalanine.
ESMS: m/z 519 ([M-H]$^-$).

Example 22. N-(2,6-Dichlorobenzoyl)-4-[2-(*tert* butoxycarbonylamino)phenyl]-L-phenylalanine.

1) 2-(*tert*-Butoxycarbonylamino)benzeneboronic acid (0.3 g) was coupled with N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine methyl ester (270 mg) by a similar procedure as described in Examples 15 to give 250 mg of N-(2,6-dichlorobenzoyl)-4-[2-(tert-butoxycarbonylamino)phenyl]-L-phenylalanine methyl ester. ESMS: m/z 543 (MH$^+$).

2) The product obtained above (40 mg) was hydrolyzed in a similar manner as described in Example 16 to give 35 mg of the title compound. ESMS: m/z 529 (MH$^+$), 527 ([M-H]$^-$).

Example 23. N-(2,6-Dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-[2-(tert-butoxycarbonylamino)phenyl]-L-phenylalanine methyl ester (90 mg) was treated with TFA (1 mL) for 2 h at room temperature. Excess TFA was removed in vacuo to give N-(2,6-dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester TFA salt.

2) The resulting TFA salt was hydrolyzed in a similar manner as described in Example 16 to give 57 mg of the title compound. ESMS: m/z 429 (MH^+)

Example 24. N-(2,6-Dichlorobenzoyl)-4-[2-(methanesulfonylamino)phenyl]-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester TFA salt (90mg) was dissolved in dry CH_2Cl_2 (5 mL). To this solution was added Et_3N (85 µL) and MsCl (30 µL). The mixture was stirred at room temperature for 3 h and diluted with water. The organic phase was dried ($MgSO_4$) and evaporated to give N-(2,6-dichlorobenzoyl)-4-[2-(methanesulfonylamino)phenyl]-L-phenylalanine methyl ester.

2) The product obtained above was hydrolyzed in a similar manner as described in Example 16 to give 70 mg of the title compound: ESMS: m/z 507 (MH^+).

Example 25. N-(2,6-Dichlorobenzoyl)-4-[2-(acetylamino)]phenyl]-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester TFA salt (90 mg) was dissolved in dry THF (5 mL). Ac_2O (60 µL) and DIEA (160µL) were added and the mixture was stirred at room temperature for 12 h. EtOAc was added and the resulting mixture was extracted with water. The organic phase was dried ($MgSO_4$) and

evaporated to give N-(2,6-dichiorobenzoyl)-4-[2-(acetylamino)]phenyl]-L-phenylalanine methyl ester.

2) The product obtained above was hydrolyzed in a similar manner as described in Example 16 to give 60 mg of the title compound; ESMS: m/z 471 (MH^+).

Example 26. N-(2,6-Dichlorobenzoyl)-4-[2-(methoxycarbonylamino)phenyl]-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester TFA salt (90 mg) was dissolved in THF (5 mL) and to this solution was added DIEA (160μL) and ClCOOMe (20μL). The mixture was stirred at room temperature for 12 h. After usual work-up as shown in Example 25, N-(2,6-dichlorobenzoyl)-4-[2-(methoxycarbonylamino)phenyl]-L-phenylalanine methyl ester was obtained.

2) The product obtained above was hydrolyzed in a similar manner as described in Example 16 to give 70 mg of the title compound; ESMS: m/z 487 (MH^+).

Example 27. N-(2,6-Dichlorobenzoyl)-4-[2-(N,N-dimethylamino)phenyl]-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester TFA salt (90 mg) was dissolved in EtOH (5 mL). To this solution was added formalin (96μL), 1 N HCl (234 μL) and $NaCNBH_3$ (36 mg). The mixture was stirred for 0.5 h at room temperature, then a 1:1 mixture of EtOH (0.5 mL) and 1N HCl (0.5 mL) was added and the mixture was stirred overnight. Additional 1N HCl was added and the mixture was stirred for 0.5 h. The mixture was neutralized with $NaHCO_3$ and extracted with EtOAc. The combined extracts were dried ($MgSO_4$) and evaporated to give N-(2,6-dichlorobenzoyl)-4-[2-(N,N-dimethylamino)phenyl]-L-phenylalanine methyl ester.

2) The product obtained above was hydrolyzed in a similar manner as described in Example 16 to give 70 mg of the title compound. ESMS: m/z 457 (MH^+).

Example 28. N-(2,6-Dichlorobenzoyl)-4-(2-ureidophenyl)-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-aminophenyl)-L-phenylalanine methyl ester TFA salt (90 mg) was dissolved in dry THF (5 mL). To this solution was added chlorosulfonyl isocyanate (22 µL) and the mixture was stirred at room temperature for 2 h. The mixture was neutralized with $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and evaporated.

2) The residue was hydrolyzed in a similar manner as described in Example 16 to give, after HPLC purification (60% MeCN, 0.1% CF_3COOH, 40 % H_2O), 30 mg (34 %) of the title compound; ESMS: m/z 472 (MH^+).

Example 29. N-(2,6-Dichlorobenzoyl)-4-[2-(N,N-dimethylamino)-6-methoxyphenyl]-L-phenylalanine.

1) 2-Methoxy-6-(N,N-dimethylamino)benzene boronic acid was coupled with N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine methyl ester to give N-(2,6-dichlorobenzoyl)-4-[2-(N,N-dimethylamino)-6-methoxyphenyl]-L-phenylalanine methyl ester. The preparation of the boronic acid and the coupling reaction was carried out in a similar manner as described in Example 7.

2) The product obtained above was hydrolyzed in a similar manner as described in Example 7 to give the title compound; ESMS: m/z 487 (MH^+).

Example 30. N-(2,6-Dichlorobenzoyl)-4-(2-hydroxyphenyl)-L-phenylalanine.

1) BBr_3 (1 mL, 1M in CH_2Cl_2) was added to a CH_2Cl_2 (10 mL) solution of N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (0.215 g) at 0 ^{0}C with stirring and the solution was slowly warmed to room temperature. The mixture was stirred for 3 h and quenched with EtOH. The solvent was removed and the residue was taken up in EtOAc. The solution was washed with satd. $NaHCO_3$ followed by brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: hexanes/ EtOAc 2:1) to yield 0.105 g of N-(2,6-dichlorobenzoyl)-4-(2-hydroxyphenyl)-L-phenylalanine methyl ester. ESMS: m/z 444 (MH^+).

2) To a solution of the product obtained above (0.03 g) in THF/MeOH (2 mL/ 0.2 mL) was added a solution of LiOH (monohydrate, 4 mg) in 0.2 mL of water and the mixture was stirred for 3 h at room temperature. The solvent was removed and the residue was dissolved in water. The mixture was acidified to pH . 2 with 1N HCl and the precipitated solid was collected by filtration, washed with water and air dried to give 0.025 g of the title compound. ESMS: m/z 430 (MH^+).

Example 31. N-(2,6-Dichlorobenzoyl)-4-(2-hydroxy-6-methoxyphenyl)-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine, ethyl ester (0.16 g, prepared in a fashion similar to that of the methyl ester described in Example 8) was dissolved in anhydrous CH_2Cl_2 (8 mL). The solution was cooled to -78 °C and BBr_3 (0.56 mL, 1 M solution in CH_2Cl_2) was added. The mixture was allowed to warm to 0 °C, and stirred at that temperature for 2 h. The mixture was subsequently warmed to room temperature and quenched with satd. $NaHCO_3$ (5 mL). The mixture was stirred for 1 h, and diluted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and

concentrated. The residue was purified by flash column chromatography (silica gel; eluent: EtOAc/hexanes 1:2) to give 40 mg of N-(2,6-dichlorobenzoyl)-4-(2-hydroxy-6-methoxyphenyl)-L-phenylalanine ethyl ester. ESMS: m/z 488 (MH^+).

2) The product obtained above (0.04 g) was hydrolyzed in a similar manner as described in Example 1 to give 35 mg of the title compound. ESMS: m/z 460 (MH^+).

Example 32. N-(2,6-Dichlorobenzoyl)-4-[2-(carboxymethoxy)-phenyl]-L-phenylalanine.

1) To a solution of the product obtained in Example 30-1) (0.1 g) in DMF (2 mL) under N_2 was added Cs_2CO_3 (0.11 g) and the mixture was stirred for 30 min. A solution of $BrCH_2CO_2Me$ (61 mL) in 1 mL of DMF was added and the mixture was heated at 50 ^0C for 6 h. DMF was removed and the residue was partitioned between EtOAc and water. The EtOAc layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: hexanes /EtOAc 1:1) to give 0.86 mg of N-(2,6-dichlorobenzoyl)-4-[2-(methoxycarbonylmethoxy)-phenyl]-L-phenylalanine methyl ester. ESMS: m/z 516 (MH^+).

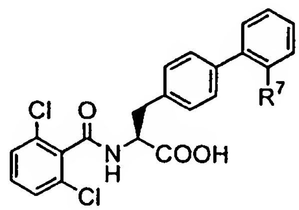
2) The product obtained above (0.86 g) was hydrolyzed in a similar manner as described in Example 1 to give 0.6 g of the title compound. ESMS: m/z 488 (MH^+).

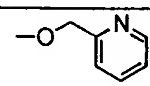
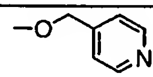
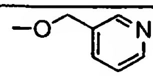
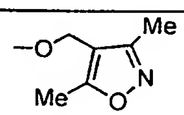
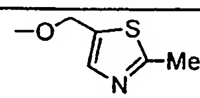
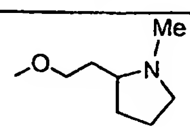
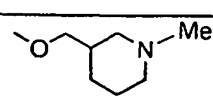
Example 33. N-(2,6-Dichlorobenzoyl)-4-[2-(cyanomethoxy)phenyl]-L-phenylalanine methyl ester

The title compound was prepared in a similar manner as described for Example 32 starting from N-(2,6-dichlorobenzoyl)-4-(2-hydroxyphenyl)-L-phenylalanine methyl ester and bromoacetonitrile. ESMS: m/z 483 (MH^+).

The following compounds were obtained in an analogous manner starting from N-(2,6-dichlorobenzoyl)-4-(2-hydroxyphenyl)-L-phenylalanine methyl ester and reacting with requisite halides.

TABLE 1



Examples	R^7	m/z (MH^+)
34	$-O(CH_2)_3CH_3$	486
35	$-OCH_2CH(Me)_2$	486
36	$-O(CH_2)_3CO_2H$	516
37	$-O(CH_2)_3OH$	488
38		521
39		521
40		521
41		539
42		541
43		541
44		541

Example 45. N-(2,6-Dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine methyl ester was synthesized by following the sequences similar to Example 1 but replacing 2-methoxy-benzeneboronic acid with 2-formylbenzeneboronic acid. ESMS: m/z 456 (MH^+).

2) The product obtained above (50.4 mg) was dissolved in a mixture of THF (1.33 mL) and MeOH (220 µL). 1M LiOH (220 µL) was added and the resulting mixture was stirred at room temperature under N_2 for 2 h. Water was then added and the mixture was acidified (approximately pH 2) with 1N HCl, extracted with EtOAc, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: $CHCl_3$ then $CHCl_3$/MeOH 10:1) to give the title compound (46.8 mg). ESMS: m/z 442 (MH^+).

Example 46. N-(2,6-Dichlorobenzoyl)-4-[2-[(phenylamino)methyl]phenyl]-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine methyl ester (49.1 mg) was dissolved in a mixture of anhydrous MeOH (1 mL) and anhydrous THF (0.5 mL). Aniline (58.8 µL), HCl (53.8 µL of 4M in dioxane) and 3Å molecular sieves were then added and the mixture was stirred under N_2 at room temperature for 1 h. $NaCNBH_3$ (4.06 mg) was added and the mixture was stirred for an additional 72 h. The pH of the mixture was brought to approximately 2 with 1N HCl to quench the reaction. The mixture was diluted with water and neutralized with 1M KOH. This was then extracted with CH_2Cl_2 and the combined organic extracts were dried (K_2CO_3) and evaporated. The residue was purified by preparative TLC (silica gel) using CH_2Cl_2 as eluent to give N-(2,6-dichlorobenzoyl)-4-[2-

[(phenylamino)methyl]phenyl]-L-phenylalanine methyl ester (21.2 mg). ESMS: m/z 533 (MH^+).

2) The product obtained above (21.2 mg) was hydrolyzed in a similar manner as described for Example 1. The mixture was acidified to pH 4-5 with AcOH, extracted with EtOAc (5 x 20 mL), dried ($MgSO_4$) and evaporated. The residue was purified by silica gel column using $CHCl_3$/MeOH (10:1) as an eluent to give the title compound. ESMS: m/z 519 (MH^+).

The following compounds (Examples 47 and 48) were prepared in a similar manner as described in Example 46.

Example 47. N-(2,6-Dichlorobenzoyl)-4-[2-(aminomethyl)phenyl]-L-phenylalanine. ESMS: m/z 443 (MH^+).

Example 48. N-(2,6-Dichlorobenzoyl)-4-[2-[(benzylamino)methyl]phenyl]-L-phenylalanine. ESMS: m/z 533 (MH^+).

Example 49. N-(2,6-Dichlorobenzoyl)-4-[2-(2-carboxyethenyl)phenyl]-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine methyl ester (51.7 mg) and (triphenylphosphoranylidene)acetic acid methyl ester (75.8 mg) were dissolved in anhydrous toluene (1 mL) and stirred at 80 °C under N_2 for 18 h. The mixture was allowed to cool and purified by preparative TLC (silica gel) using hexanes/EtOAc (2:1) as eluent to give N-(2,6-dichlorobenzoyl)-4-[2-[2-(methoxycarbonyl)ethenyl]phenyl]-L-phenylalanine methyl ester (48.0 mg). ESMS: m/z 512 (MH^+).

2) The product obtained above (26.4 mg) was hydrolyzed with 5 eq. of $LiOH \cdot H_2O$ in a similar manner as described in

Example 1 to give the title compound as a mixture of trans and cis isomers (4:1) (22.0 mg). ESMS: m/z 484 (MH^+).

Example 50. N-(2,6-Dichlorobenzoyl)-4-[2-(hydroxymethyl)phenyl]-L-phenylalanine.

1) $NaBH_4$ (21 mg) was added to a solution of N-(2,6-dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine methyl ester (0.23 g) in MeOH (5 mL) and the mixture was stirred at room temperature for 3 h. The reaction was quenched with acetone and the mixture was evaporated. The residue was partitioned between EtOAc and water. The EtOAc layer was dried ($MgSO_4$) and evaporated to yield N-(2,6-dichlorobenzoyl)-4-[2-(hydroxymethyl)phenyl]-L-phenylalanine methyl ester (0.24 g). ESMS: m/z 480 ($[M+Na]^+$).

2) The product obtained above was hydrolyzed in a similar manner as described for Example 1 to give the title compound (0.2 g). ESMS: m/z 450 ($[M+Li]^+$).

Example 51. N-(2,6-Dichlorobenzoyl)-4-[2-(methoxymethyl)phenyl]-L-phenylalanine.

1) A mixture of N-(2,6-dichlorobenzoyl)-4-[2-(hydroxymethyl)phenyl]-L-phenylalanine methyl ester (0.15 g), CBr_4 (0.22 g) and PPh_3 (0.173 g) in CH_2Cl_2 (5 mL) was stirred at room temperature for 18 h. The solvent was evaporated and the residue was purified by flash column chromatography (silica gel; eluent: CH_2Cl_2 /EtOAc 9:1 to 8:1) to yield 0.12 g of N-(2,6-dichlorobenzoyl)-4-[2-(bromomethyl)phenyl]-L-phenylalanine methyl ester. ESMS: m/z 522 (MH^+).

2) A mixture of the product obtained above (0.04 g) and NaOMe (0.04 g) in DMF (3 mL) was stirred at room temperature for 18 h. DMF was removed and the residue was partitioned between EtOAc and water. The aqueous layer was separated, adjusted to pH 4 with 1N HCl and extracted with

EtOAc. The EtOAc layer was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by HPLC (60% MeCN, 0.1% CF_3COOH, 40 % H_2O) to give 9.4 mg of the title compound. ESMS: m/z 480 ($[M+Na]^+$).

Example 52. N-(2,6-Dichlorobenzoyl)-4-(2-carboxyphenyl)-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-formylphenyl)-L-phenylalanine methyl ester (104 mg) was dissolved in acetone (700 µL) by warming up to about 40 °C. A warm (40 °C) solution of $KMnO_4$ (61.2 mg) in a mixture of acetone (900 µL) and water (130 µL) was then added over a 1 h period and the resulting mixture was stirred at that temperature for an additional 2h. The mixture was filtered through Celite and washed with acetone. The filtrate was taken up with water and acidified to approximately pH 2 with 1N HCl, and extracted with EtOAc. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified through a silica gel column using toluene then a gradient of toluene/EtOAc (20:1 to 3:1) as an eluent to give N-(2,6-dichlorobenzoyl)-4-(2-carboxyphenyl)-L-phenylalanine methyl ester (85.0 mg). ESMS: m/z 472 (MH^+).

2) The product obtained above was hydrolyzed in a similar manner as described for Example 1 to give the title compound (34.1 mg). ESMS: m/z 458 (MH^+).

Example 53. N-(2,6-Dichlorobenzoyl)-4-[2-(N-benzylcarbamoyl) phenyl]-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-carboxyphenyl)-L-phenylalanine methyl ester (51.9 mg) was dissolved in anhydrous DMF (1 mL) and EDC (25.3 mg), HOBT (20.2 mg), DIEA (28.7 µL) and benzylamine (14.4 µL) were added. The resulting mixture was stirred at room temperature under N_2 for 20 h, diluted with EtOAc and washed with 1N HCl, satd.

$NaHCO_3$, water and brine. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified through a silica gel column using hexanes/EtOAc (1:1 to 1:2) as an eluent to give N-(2,6-dichlorobenzoyl)-4-[2-(N-benzylcarbamoyl)phenyl]-L-phenylalanine methyl ester (48.9 mg). ESMS: m/z 561 (MH^+).

2) The product obtained above was hydrolyzed in a similar manner as described for Example 1 to give the title compound (34.2 mg). ESMS: m/z 547 (MH^+).

The following compounds (Example 54-59) were prepared in an analogous manner as described in Example 53.

Example 54. N-(2,6-Dichlorobenzoyl)-4-[2-(N-methylcarbamoyl)phenyl]-L-phenylalanine. ESMS: m/z 471(MH^+).

Example 55. N-(2,6-Dichlorobenzoyl)-4-[2-(N-n-butylcarbamoyl)phenyl]-L-phenylalanine. ESMS: m/z 513(MH^+).

Example 56. N-(2,6-Dichlorobenzoyl)-4-[2-[N-(2-hydroxyethyl)carbamoyl]phenyl]-L-phenylalanine. ESMS: m/z 501(MH^+).

Example 57. N-(2,6-Dichlorobenzoyl)-4-[2-[N-(3-hydroxypropyl)carbamoyl]phenyl]-L-phenylalanine. ESMS: m/z 515 (MH^+).

Example 58. N-(2,6-Dichlorobenzoyl)-4-[2-(N,N-dimethyl carbamoyl)phenyl]-L-phenylalanine. ESMS: m/z 485 (MH^+).

Example 59. N-(2,6-Dichlorobenzoyl)-4-[2-[N-(2-morpholinoethyl)carbamoyl]phenyl]-L-phenylalanine. ESMS: m/z 570 (MH^+).

Example 60. N-(2,6-Dichlorobenzoyl)-4-[2-(carbamoyl)phenyl)]-L-phenylalanine.

1) N-(2,6-dichlorobenzoyl)-4-(2-carboxyphenyl)-L-phenylalanine methyl ester (52.6 mg) was dissolved in anhydrous THF (1 mL), carbonyldiimidazole (36.1 mg) was added and the mixture was stirred at room temperature under N_2 for 2 h. Ammonium hydroxide (29% aqueous solution, 135 µL) was added and the mixture was stirred for an additional 22 h. The mixture was then extracted with EtOAc. The extract was washed with 1N HCl, sat. $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated. The residue was purified through a silica gel column using toluene/EtOAc (1:1) as an eluent to give N-(2,6-dichlorobenzoyl)-4-(2-carbamoylphenyl)-L-phenylalanine methyl ester (48.1 mg). ESMS: m/z 471 (MH^+).

2) The product obtained above was hydrolyzed with 3 eq. of LiOH in a similar manner as described in Example 1 to give the title compound (41.6 mg). ESMS: m/z 457 (MH^+).

Example 61. N-(2,6-Dichlorobenzoyl)-4-[2-[(N-methanesulfonyl)carbamoyl]phenyl]-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2-carboxyphenyl)-L-phenylalanine methyl ester (57.0 mg) was dissolved in anhydrous THF (1 mL), carbonyldiimidazole (23.5 mg) was added and the mixture was stirred at room temperature under N_2 for 2 h. Methanesulfonamide (17.2 mg) and DBU (27 µL) were added and the mixture was stirred for an additional 18 h. The mixture was then heated to 40 °C, stirred for 7 h at the same temperature, cooled to room temperature, diluted with EtOAc, washed with 1N HCl and then brine, dried ($MgSO_4$) and evaporated. The residue was purified by preparative TLC (silica gel) using CH_2Cl_2/MeOH (100:1 to 10:1) as an eluent to give N-(2,6-dichlorobenzoyl)-4-[2-[N-

(methanesulfonyl)carbamoyl]phenyl]-L-phenylalanine methyl ester (37.0 mg). ESMS: m/z 549 (MH^+).

2) The product obtained above was hydrolyzed with 3 eq. of LiOH in a similar manner as described in Example 1 to give the title compound (36 mg). ESMS: m/z 535 (MH^+).

Example 62. N-(2-Chloro-4-nitrobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) N-(2-Chloro-4-nitrobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester was prepared in a similar fashion to that described in Example 1-1), 2), 3) and 4) but replacing 2,6-dichlorobenzoyl chloride with 2-chloro-4-nitrobenzoyl chloride.

2) The methyl ester obtained above was then hydrolyzed in a similar manner as described for Example 1-5) to yield the title compound. ESMS: m/z 455 (MH^+).

Example 63. N-(4-Amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) Ra-Ni (0.4 mL of 50% dispersion in water) was added to a solution of N-(2-chloro-4-nitrobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (1.04 g) in anhydrous MeOH (50 mL) and the mixture was stirred at room temperature under H_2 atmosphere for 3.5 h. The mixture was then filtered over Celite and washed with MeOH. The filtrate was evaporated and the residue was purified by flash column chromatography (silica gel; eluent: CH_2Cl_2/MeOH 100:1 to 20:1) to give N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (887 mg). ESMS: m/z 439 (MH^+). The product obtained above was also prepared via the coupling of 4-(2-methoxyphenyl)-L-phenylalanine methyl ester hydrochloride with 4-amino-2-chlorobenzoic acid using EDC and HOBT in an analogous manner as described in Example 2.

2) The product obtained above (57.0 mg) was hydrolyzed with LiOH in THF/MeOH mixture in a similar manner as described in Example 1-5). The solvent was removed, and the residue was dissolved in water. The mixture was acidified to approximately pH 5 with 10% citric acid, extracted with EtOAc, dried ($MgSO_4$) and evaporated. The residue was purified through a silica gel column using $CHCl_3$/MeOH (10:1) as an eluent to give the title compound (53.9 mg). ESMS: m/z 425 (MH^+).

Example 64. N-[2-Chloro-4-(methanesulfonylamino)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

1) $MeSO_2Cl$ (24 µL) was added to a solution of N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (56.0 mg) in anhydrous CH_2Cl_2 (1 mL) containing DIEA (66.6 µL). The resulting mixture was stirred at room temperature under N_2 for 3 h and diluted with CH_2Cl_2, washed with 1N HCl, water, dried ($MgSO_4$) and evaporated. The residue was purified through a silica gel column using CH_2Cl_2 as an eluent to give N-[2-chloro-4-(N,N-dimethanesulfonylamino)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (59.4 mg). ESMS: m/z 595 (MH^+).

2) The product obtained above was hydrolyzed with 3 eq. of LiOH in a similar manner as described in Example 1-5) to give the title compound(43.4 mg). ESMS: m/z 503 (MH^+).

The following compounds (Examples 65-68) were prepared in an analogous manner as described in Example 64.

Example 65. N-[2-Chloro-4-(trifluoromethanesulfonylamino) benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine. ESMS: m/z 557 (MH^+). $MeSO_2Cl$ was replaced by CF_3SO_2Cl.

Example 66. N-[2-Chloro-4-(ethoxycarbonylamino)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine. ESMS: m/z 497(MH^+). $MeSO_2Cl$ was replaced by EtOCOCl.

Example 67. N-[2-Chloro-4-(acetylamino)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine. ESMS: m/z 467(MH^+). $MeSO_2Cl$ was replaced by AcCl.

Example 68. N-[2-Chloro-4-(benzenesulfonylamino)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine. ESMS: m/z 565 (MH^+). $MeSO_2Cl$ was replaced by $PhSO_2Cl$.

Example 69. N-(2-Chloro-4-ureidobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) Chlorosulfonylisocyanate (16.4 μL) was added to a solution of N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (55.2 mg) in anhydrous MeCN (1 mL) and the mixture was stirred at room temperature under N_2 for 1 h. Satd. $NaHCO_3$ (40 mL) was added slowly and the mixture was extracted with EtOAc. The extracts were combined, dried ($MgSO_4$) and evaporated. The residue was purified by preparative TLC (silica gel) using $CHCl_3$/MeOH as an eluent.

2) The product obtained above was hydrolyzed with LiOH in a similar manner as described in Example 64 to yield the title compound (24 mg). ESMS: m/z 468 (MH^+).

Example 70. N-[2-Chloro-4-(3-methylthioureido)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

1) Methylisothiocyanate (43 μL) was added to a solution of N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (55.1 mg) in anhydrous DMF (1 mL) containing DIEA (22 μL) and DMAP (catalitic amount). The resulting mixture was then heated

at 90 °C under N_2 for 1 d. After cooling, the mixture was diluted with EtOAc, washed sequentially with 1N HCl, satd. $NaHCO_3$ and water, dried ($MgSO_4$) and evaporated. The residue was purified by preparative TLC (silica gel) using CH_2Cl_2/MeOH (15:1) as an eluent to give N-[2-chloro-4-(3-methylthioureido)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (22.7 mg). ESMS: m/z 512 (MH^+).

2) The product obtained above was hydrolyzed in a similar manner as described in Example 64 to the title compound (22.0 mg). ESMS: m/z 498 (MH^+).

Example 71. 3-Acetyl-N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) 3-Acetyl-L-tyrosine ethyl ester was prepared by bubbling HCl gas into a solution of 3-acetyl-L-tyrosine (5 g) in ethanol (30 mL). Di-tert-butyl dicarbonate (5 g) was added to a solution of 3-acetyl-L-tyrosine ethyl ester (5 g) in THF (50 mL) and DIEA (10 mL) and the mixture was stirred overnight at room temperature. THF was removed and the residue was partitioned between water and CH_2Cl_2. The organic layer was separated, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: hexanes/EtOAc, 4:1) to yield N-(tert-butoxycarbonyl)-3-acetyl-L-tyrosine ethyl ester (4.3 g). ESMS: m/z 352 (MH^+).

2) Anhydrous pyridine (1.1 mL, 12.82 mmol) was added with stirring to a solution of the product obtained above (1.5 g) in CH_2Cl_2 (15 mL) at 0 °C. Triflic anhydride (1.1 mL) was added dropwise and the mixture was warmed slowly to room temperature and allowed to stir for 24 h. The mixture was diluted with CH_2Cl_2, washed sequentially with 1 N HCl, brine, satd $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give N-(tert-butoxycarbonyl)-3-acetyl-O-(trifluoromethanesulfonyl)-L-tyrosine ethyl ester (2.5 g). ESMS: m/z 506 ($[M+Na]^+$).

3) A solution of the product obtained above (0.3 g) in toluene (3 mL) was added with stirring to a solution of 2-methoxybenzeneboronic acid (0.13 g) K_2CO_3 (0.25 g) in toluene / DMF (4/1 mL) under N_2. $Pd(PPh_3)_4$ (0.14 g) was added and the mixture was heated at 85 °C for 48 h. The mixture was cooled, filtered and the solvent was evaporated. The residue was dissolved in EtOAc, washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: hexanes/EtOAc, 2.5:1) to yield 0.18 g of 3-acetyl-N-(tert-butoxycarbonyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester. ESMS: m/z 442 (MH^+).

4) A solution of the product obtained above (0.18 g) in TFA/ CH_2Cl_2 (8 mL, 50% v/v) was stirred at room temperature for 1 h. The solution was evaporated and dried under high vacuum to give a TFA salt of 3-acetyl-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester.

5) To an ice-cold solution of the TFA salt obtained above in CH_2Cl_2 (2 mL) was added DIEA (213 µL) followed by a solution of 2,6-dichlorobenzoyl chloride (65 mL) in CH_2Cl_2 (7 mL). The mixture was warmed to room temperature and allowed to stir for 24 h. After the usual work-up as described in Example 1-4) the crude material was purified by flash column chromatography (silica gel; eluent: hexanes/EtOAc, 3:1) to yield 0.142 g of 3-acetyl-N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester. ESMS: m/z 514 (MH^+).

6) The product obtained above (0.05 g) was hydrolyzed with LiOH in a similar procedure as described in Example 1-5) to yield 46.5 mg of the title compound. mp. 87-89 °C; ESMS: m/z 486(MH^+).

Example 72. 3-Acetyl-N-(2,6-dichlorobenzoyl)-4-phenyl-L-phenylalanine.

By substituting 2-methoxybenzeneboronic acid with benzeneboronic acid, the title compound was obtained as a solid in a similar manner as described in Example 71. mp. 109-111 °C; MS: m/z 456 (MH^+).

Example 73. N-(2,6-Dichlorobenzoyl)-3-(1-hydroxyethyl)-4-(2-methoxyphenyl)-L-phenylalanine.

1) $NaBH_4$ (12 mg) was added to a solution of 3-acetyl-N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (0.1 g) in MeOH (3 mL) and the mixture was stirred at room temperature for 2 h. The mixture was quenched with 1 N HCl and extracted with CH_2Cl_2. The extract was washed successively with 1 N HCl and brine, dried and evaporated. The residue was purified by a flash column chromatography (silica gel; eluent: hexanes/EtOAc 3:1) to yield 45 mg of N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester. ESMS: m/z 516 (MH^+).

2) The product obtained above (0.040 g) was hydrolyzed with LiOH in a similar manner as described in Example 1-5) to yield 28 mg of the title compound. MS: m/z 488(MH^+).

Example 74. N-(2,6-Dichlorobenzoyl)-3-(1-hydroxyethyl)-4-phenyl-L-phenylalanine.

The title compound was prepared from 3-acetyl-N-(2,6-dichlorobenzoyl)-4-phenyl-L-phenylalanine ethyl ester in a similar fashion as described in Example 73. mp. 115-117 °C. MS: m/z 458 (MH^+).

Example 75. N-(2,6-Dichlorobenzoyl)-3-methoxy-4-(2-methoxyphenyl)-L-phenylalanine.

1) 3,4-Dihydroxy-L-phenylalanine methyl ester was prepared by bubbling HCl into a solution of 3,4-dihydroxy-L-phenylalanine (10 g) in methanol (100 mL). Di-tert-butyl dicarbonate (12.1 g) was added to a solution of the ester

in THF (250 mL) and DIEA (35.4 mL) and the mixture was warmed for 5 minutes and stirred for 1 h at room temperature. THF was removed and the residue was partitioned between water and ethyl acetate. The organic layer was washed with 1N HCl, brine, dried ($MgSO_4$) and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: hexanes/EtOAc, 1:1) to yield the desired N-(tert-butoxycarbonyl)-3,4-dihydroxy-L-phenylalanine methyl ester (13.4 g). ESMS: m/z 312 (MH^+).

2) 2,6-Dichlorobenzyl chloride (1.73 g) was added to a suspension of N-(tert-butoxycarbonyl)-3,4-dihydroxy-L-phenylalanine methyl ester (2.5 g), K_2CO_3 (2.22 g), and n-Bu_4NI (0.297 g) in DMF (15 mL) at room temperature. The mixture was stirred overnight at room temperature, diluted with water and extracted with ether. The extract was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexanes/CH_2Cl_2/EtOAc, 5:5:1) to yield N-(tert-butoxycarbonyl)-3,4-bis(2,6-dichlorobenzyloxy)-L-phenylalanine methyl ester (2.0 g), ESMS: m/z 630 (MH^+), N-(tert-butoxycarbonyl)-3-(2,6-dichlorobenzyloxy)-4-hydroxy-L-phenylalanine methyl ester (0.39 g), ESMS: m/z 470(MH^+), and N-(tert-butoxycarbonyl)-4-(2,6-dichlorobenzyloxy)-3-hydroxy-L-phenylalanine methyl ester (0.45 g), ESMS: m/z 470 (MH^+), respectively.

3) To a suspension of N-(tert-butoxycarbonyl)-4-(2,6-dichlorobenzyloxy)-3-hydroxy-L-phenylalanine methyl ester (0.45 g), K_2CO_3 (0.199 g), and n-Bu_4NI (0.035 g) in DMF (4.0 mL) was added CH_3I (0.072 mL) and the mixture was stirred overnight at room temperature. DMF was removed and the residue was partitioned between water and EtOAc. The organic layer was separated and the aqueous solution was extracted with EtOAc. The combined extract was dried ($MgSO_4$) and evaporated. The residue was purified by preparative TLC (silica gel; eluent: hexanes/CH_2Cl_2/EtOAc, 3:3:1) to yield 0.396 g of N-(tert-butoxycarbonyl)-4-(2,6-

dichlorobenzyloxy)-3-methoxy-L-phenylalanine methyl ester. ESMS: m/z 484 (MH^+).

4) Hydrogen gas was bubbled to a suspension of the product obtained above (0.39 g), and 10% Pd on activated carbon (0.05 g) in methanol (10 mL) overnight at room temperature. The catalyst was filtered over Celite and the filtrate was evaporated. The residue was purified by preparative TLC (silica gel; eluent: CH_2Cl_2/MeOH, 10:1) to yield 0.21 g of N-(tert-butoxycarbonyl)-4-hydroxy-3-methoxy-L-phenylalanine methyl ester. ESMS: m/z 348 ($[M+Na]^+$).

5) Anhydrous pyridine (0.15 mL) was added with stirring to a solution of the product obtained above (0.2 g) in CH_2Cl_2 (3.0 mL) at 0°C. Triflic anhydride (0.16 mL) was added dropwise and the mixture was warmed slowly to room temperature and allowed to stir for 3 hours at room temperature. The mixture was diluted with CH_2Cl_2 and washed sequentially with 1N HCl, brine, saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), and evaporated to give N-(tert-butoxycarbonyl)-3-methoxy-4-trifluoromethanesulfonyloxy-L-phenylalanine methyl ester (0.28 g). ESMS: m/z 457 ($[M+Na]^+$).

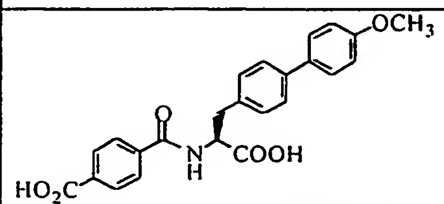
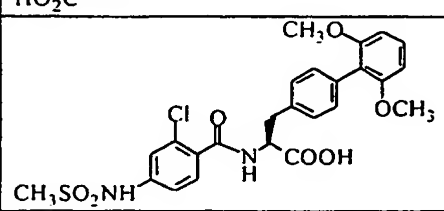
6) A solution of the product obtained above (0.28 g) in DME (2.0 mL) was added to a solution of 2-methoxybenzene boronic acid (0.112 g), K_2CO_3 (0.21 g) in DME (2.0 mL) under N_2. $Pd(PPh_3)_4$ (0.12 g) was added and the mixture was heated at 65 °C for 48 h, cooled, filtered and the solvent was evaporated. The residue was extracted with EtOAc and the extract was washed with water, dried and evaporated. The residue was purified by preparative TLC (silica gel; eluent: hexanes/EtOAc, 3:1) to yield 0.02 g of N-(tert-butoxycarbonyl)-3-methoxy-4-(2-methoxyphenyl)-L-phenylalanine methyl ester. ESMS: m/z 438 ($[M+Na]^+$).

7) A mixture of the product obtained above (0.055 g) in TFA/CH_2Cl_2 (1 mL, 50% v/v) was stirred at room temperature for 1 h, evaporated and dried under high vacuum. To an ice-cold solution of the residue in CH_2Cl_2 (2 mL) was added DIEA (0.069 mL) followed by a solution of 2,6-dichlorobenzoyl chloride (0.02 mL) in CH_2Cl_2 (1 mL). The mixture was warmed to room temperature and allowed to stir for overnight. After the usual work-up in a similar manner as shown in Example 1, the crude material was purified by preparative TLC (silica gel; eluent: hexanes/EtOAc, 2:1) to yield 0.04 g of N-(2,6-dichlorobenzoyl)-3-methoxy-4-(2-methoxyphenyl)-L-phenylalanine methyl ester. ESMS: m/z 488 (MH^+).

8) The product obtained above (0.04 g) was hydrolyzed with LiOH in a similar procedure as described in Example 1-5) to yield 17.8 mg of the title compound. mp. 100-102 °C. ESMS: m/z 474 (MH^+).

The following compounds were prepared from the corresponding materials in a similar manner as described in one of above Examples.

TABLE 2

Example	chemical structure	m/z (MH^+)
76		419
77		533

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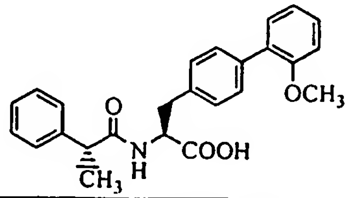
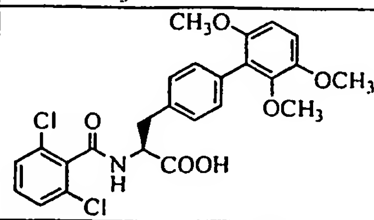
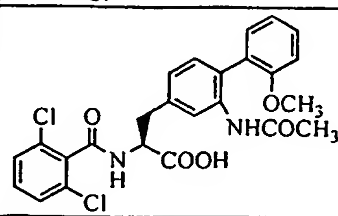
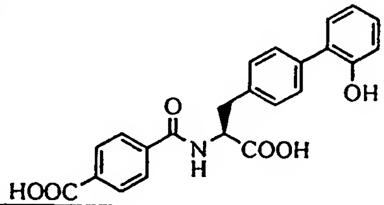
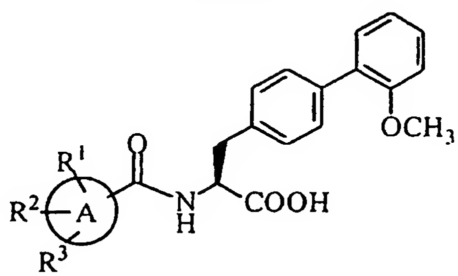
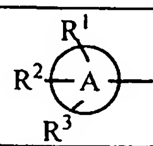
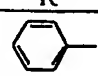
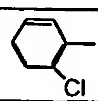
78		403
79		518
80		501
81		405 (M^+)

TABLE 3



Example		m/z (MH^+)
82		375
83		410

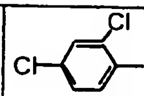
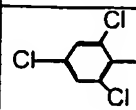
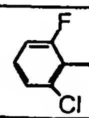
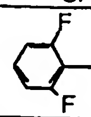
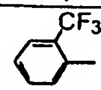
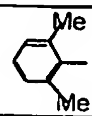
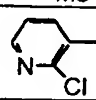
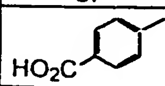
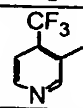
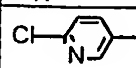
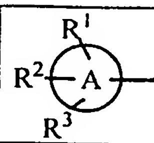
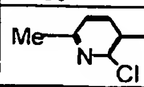
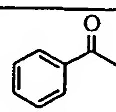
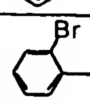
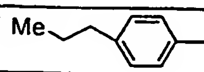
84		444
85		479
86		428
87		411
88		444
89		402
90		411
91		419
92		444
93		411

Table 3 (continued)

Example		m/z (MH^+)
94		425
95		403 (M^+)
96		454
97		417 (M^+)

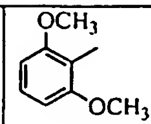
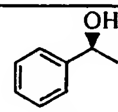
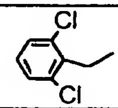
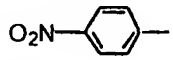
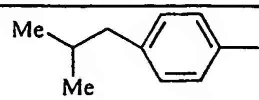
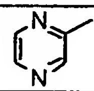
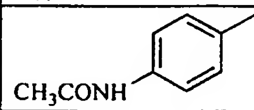
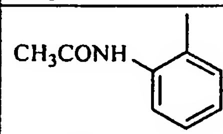
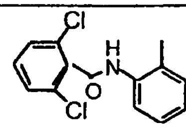
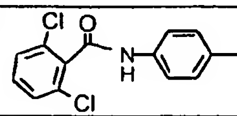
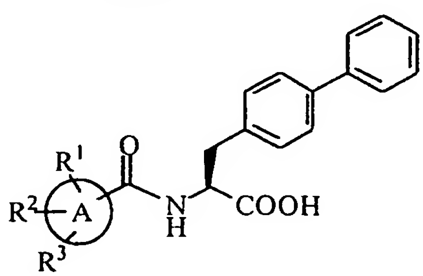
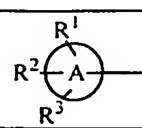
98		435 (M^+)
99		405 (M^+)
99		458
101		420 (M^+)
102		432
103		377 (M^+)
104		433
105		433
106		563
107.		563

TABLE 4



Example		m/z (MH^+)

SUBSTITUTE SHEET (RULE 26)

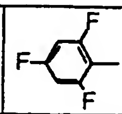
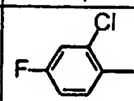
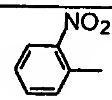
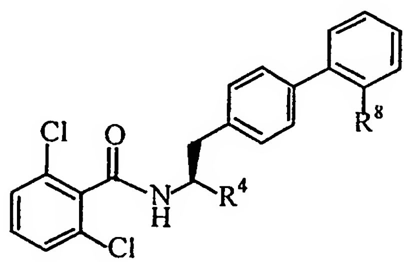
108		399
109		398
110		390 (M^+)

TABLE 5



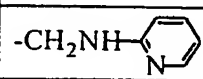
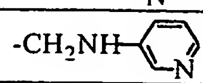
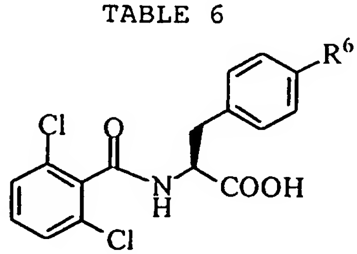
Example	R^8	R^4	m/z (MH^+)
111	-H	-COOH	414
112	-Me	-COOH	428
113	$-CF_3$	-COOH	481
114	$-CH_2NHCH_2Ph$	-COOMe	547
115		COOMe	534
116		COOMe	534

TABLE 6



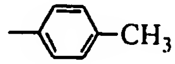
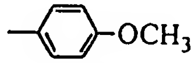
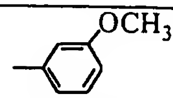
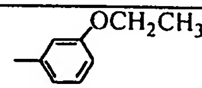
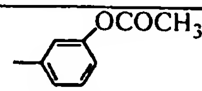
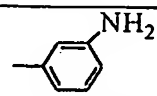
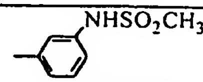
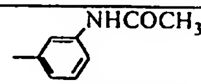
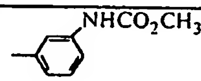
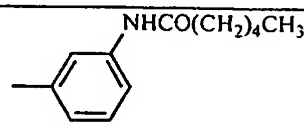
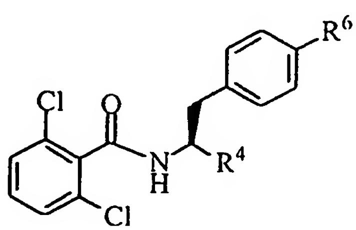
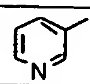
Example	R^6	m/z (MH^+)
117		428
118		444
119		444
120		458
121		456
122		429
123		507
124		471
125		487
126		527

TABLE 7



Example	R^6	R^4	m/z (MH^+)
127		COOMe	429

SUBSTITUTE SHEET (RULE 26)

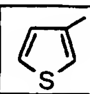
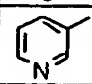
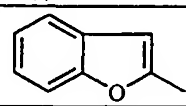
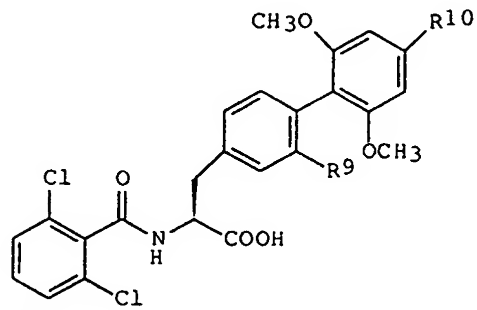
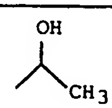
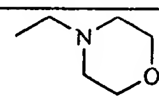
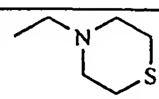
128		COOH	420
129		COOH	415
130		COOH	454

TABLE 8



Example	R^9	R^{10}	m/z (MH^+)
131		H	518
132	H		559
133	H		573
134	H		589

Example 135: N-(2,6-Dichlorobenzoyl)-4-(2,6-difluorophenyl)-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-O-(trifluoromethanesulfonyl)-L-tyrosine methyl ester was prepared in a similar method as described in Example 5-1) and 2).

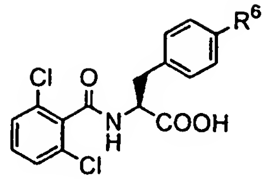
2) To a mixture of the product obtained above (3.00 g), hexamethylditin (1.96 g) and anhydrous LiCl (0.76 g) in dioxane (30 mL) under N_2 was added $Pd(PPh_3)_4$ (0.34 g) and the mixture was heated at 98 °C for 3 hours. The mixture was cooled, diluted with EtOAc, filtered through Celite and evaporated. The residue was purified by column chromatography (silica gel; eluent: EtOAc/hexane 1/3) to yield 2.46 g of N-(2,6-dichlorobenzoyl)-4-trimethylstannio-L-phenylalanine methyl ester. ESMS: m/z 516 (MH^+) and 514 $(M-H)^-$.

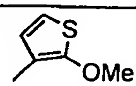
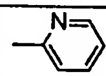
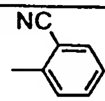
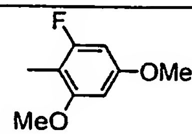
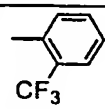
3) To a mixture of the product obtained above (0.17 g) and 1-bromo-2,6-difluorobenzene (95 mg) in toluene (2 mL) under N_2 was added $Pd(PPh_3)_4$ (0.02 g) and the mixture was heated at 110 °C for 2 hours. The mixture was evaporated. The residue was purified by column chromatography (silica gel; eluent: EtOAc/hexane 1/3) to yield 58 mg of N-(2,6-dichlorobenzoyl)-4-(2,6-difluorophenyl)-L-phenylalanine methyl ester. ESMS: m/z 464 (MH^+), 486 (M^++Na) and 562 $(M-H)^-$.

4) The product obtained above (0.058 g) was hydrolyzed with LiOH as described in Example 1-5) to yield the title compound (0.04 g). ESMS: m/z 450 (MH^+), 472 (M^++Na) and 448 $(M-H)^-$.

The following compounds (Example 136 - 140) were prepared in a similar procedure as described in Example 135 but replacing 1-bromo-2,6-difluorobenzene with the requisite bromobenzenes.

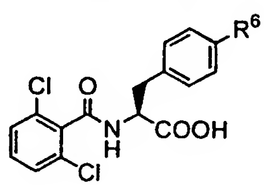
TABLE 9

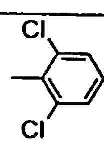


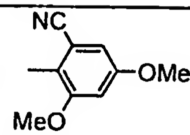
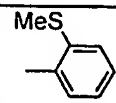
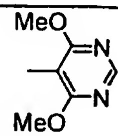
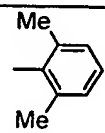
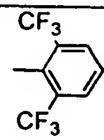
Example	R^6	MS, m/z
136		449 $(M-H)^-$
137		415 (MH^+)
138		439 (MH^+)
139		492 (MH^+)
140		498 (MH^+)

The following compounds (Example 141-146) were prepared in a similar method as described in Example 5 but replacing 2-methoxybenzeneboronic acid with the requisite benzeneboronic acids.

TABLE 10

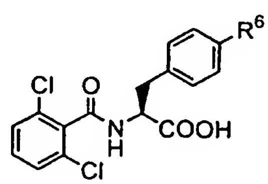


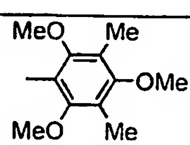
Example	R^6	MS: m/z	mp: °C
141		484 (MH^+)	

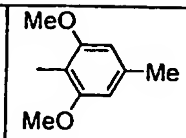
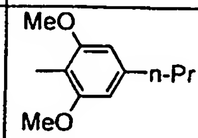
142		499 (MH^+)	
143		460 (MH^+)	
144		476 (MH^+)	
145		442 (MH^+)	200-201
146		550 (MH^+)	259-260

The following compounds (Example 147-149) were prepared in a similar method as described in Example 7 but replacing 1,3-dimethoxybenzene with the requisite benzenes.

TABLE 11



Example	R°	MS: m/z	mp: °C
147		532 (MH^+)	114-115

148		488 (MH^+)	233-234
149		516 (MH^+)	238-239 (dec.)

Example 150: N-(2,6-Dichlorobenzoyl)-4-(2-cyano-6-carbamoylphenyl)-L-phenylalanine.

1) To a mixture of 2,6-dicyanobenzene boronic acid (0.516 g) and anhydrous K_2CO_3 (0.52 g) in DME/H_2O (10 mL/0.5 mL) under N_2 was added N-(2,6-dichlorobenzoyl)-O-(trifluoromethanesulfonyl)-L-tyrosine methyl ester (0.5 g), The catalyst Pd(PPh_3)$_4$ (0.1 g) was added and the mixture was heated at 80 °C for 5 h. The mixture was cooled, diluted with EtOAc and washed successively with water and brine. The organic layer was dried ($MgSO_4$), evaporated, and the residue was purified by column chromatography (silica gel; eluent: EtOAc/hexane 3/1)) to yield 325 mg of N-(2,6-dichlorobenzoyl)-4-(2-cyano-6-carbamoyl-phenyl)-L-phenylalanine methyl ester. ESMS: m/z 496 (MH^+), 494 $(M-H)^-$.

2) The product obtained above (150 mg) was hydrolyzed with LiOH as described in Example 1-5) to yield the title compound (0.06 g). MS(m/z) 465(MH^+)

Example 151: N-(2,6-Dichlorobenzoyl)-4-(2,6-dicyanophenyl)-L-phenylalanine.

1) To a mixture of 2,6-dicyanobenzene boronic acid (0.516 g) and anhydrous K_2CO_3 (0.2 g) in toluene (10 mL) under N_2 was added N-(2,6-dichlorobenzoyl)-O-(trifluoromethanesulfonyl)-L-tyrosine methyl ester (0.5 g). Pd(PPh_3)$_4$ (0.1 g) was added and the mixture was heated at 90 °C for 8 h. The mixture was cooled, diluted with EtOAc and washed successively with water and brine. The organic layer

was dried ($MgSO_4$) and evaporated, and the residue was purified by column chromatography (silica gel; eluent: EtOAc/hexane 1/1) to yield 58 mg of N-(2,6-dichlorobenzoyl)-4-(2,6-dicyanophenyl)-L-phenylalanine methyl ester.

2) The product obtained above was hydrolyzed in a similar procedure as described in Example 1-5) to yield the title compound. MS(m/z) 482(MH^+)

Example 152: N-(2,6-Dichlorobenzoyl)-4-[2-(methylsulfonyl)phenyl]-L-phenyl-alanine **(152B)**, and N-(2,6-dichloro-benzoyl)-4-[2-(methylsulfinyl)phenyl]-L-phenylalanine **(152A and 152C).**

1) N-(2,6-Dichlorobenzoyl)-4-[2-(methylthio)phenyl]-L-phenyl-alanine methyl ester (0.35 g) was dissolved in CH_2Cl_2 (5 mL). mCPBA (50-60%, 0.255g) was added at 0 °C and the mixture was stirred at 0 °C for 2 h. The mixture was washed successively with aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: EtOAc/hexane 1/3) to yield 0.125g of N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfonyl)phenyl]-L-phenylalanine methyl ester (ESMS (m/z): 506 (MH^+), 528 (M^+ +Na), 504 (M^+ -1)) and 0.227 mg of N-(2,6-dichloro-benzoyl)-4-[2-(methylsulfinyl)phenyl]-L-phenylalanine methyl ester (a mixture of two diastereomers) (ESMS (m/z): 490 (MH^+), 512 (M^+ +Na), 488 $(M-H)^-$.

2) N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfonyl)phenyl]-L-phenylalanine methyl ester was hydrolyzed with LiOH as described in Example 1-5) to yield N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfonyl)phenyl]-L-phenylalanine (152B). ESMS: m/z 492 (MH^+), 514 (M^++Na), 491 $(M-H)^-$.

3) N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfinyl)phenyl]-L-phenylalanine methyl ester (a mixture of two diastereomers) was hydrolyzed with LiOH as

described for in Example 1-5) to yield N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfinyl)phenyl]-L-phenylalanine (a mixture of two diastereomers). The mixture was taken up in CH_2Cl_2 and the solid was collected by filtration, washed with CH_2Cl_2, and dried to yield one diastereomer of N-(2,6-dichlorobenzoyl)-4-[2-(methylsulfinyl)phenyl]-L-phenylalanine (80 mg) (**152A**). ESMS: m/z 476 (MH^+), 498 (M^++Na), 474 $(M-H)^-$. ^{1}H-NMR (DMSO-d_6): δ 2.41 (s, 3H), 2.97 (m, 1H), 3.2 (dd, 1H), 4.72 (m, 1H), 7.32 (m, 3H), 7.4 (m, 5H), 7.6-7.7 (m, 2H), 8.0 (d, 1H), 9.15 (d, 1H). The filtrate was evaporated and the residue was crystallized from EtOAc /hexane to afford the other diastereomer of N-(2,6-dichloro-benzoyl)-4-[2-(methylsulfinyl)phenyl]-L-phenylalanine (44 mg) (**152C**). ESMS: m/z 476 (MH^+), 498 (M^++Na), 474 $(M-H)^-$. ^{1}H-NMR (DMSO-d_6): δ 2.43 (s, 3H), 2.98 (m, 1H), 3.22 (m, 1H), 4.74 (m, 1H), 7.32 (m, 3H), 7.4 (m, 5H), 7.6-7.7 (m, 2H), 8.0 (d, 1H), 9.15 (d, 1H).

Example 153: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxy-3-fluorophenyl)-L-phenylalanine (153A) and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3,5-difluorophenyl)-L-phenylalanine (153B)

1) N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (232 mg) was dissolved in anhydrous MeCN (10 mL) under N_2 and 3,5-dichloro-1-fluoropyridinium triflate (85%, 353 mg) was added and the mixture was refluxed for 1 day. More 3,5-dichloro-1-fluoropyridinium triflate (175 mg) was added and the mixture was refluxed for another day. The mixture was then concentrated, and the residue was taken up with water and extracted with CH_2Cl_2. The extract was washed with sat. $NaHCO_3$, water, dried ($MgSO_4$), filtered and evaporated. The residue was purified by preparative TLC (silica gel; eluent:

hexane/AcOEt 5:1 to 2:1) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-fluorophenyl)-L-phenylalanine methyl ester(109 mg) and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3,5-difluorophenyl)-L-phenylalanine methyl ester (37 mg).

2) The two products obtained above were separately hydrolyzed in a similar method as described in Example 1-5) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-fluorophenyl)-L-phenylalanine (mp 228-229 °C; MS m/z 492 (MH^+)) (153A) and N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3,5-difluorophenyl)-L-phenylalanine (mp 201-202 °C; MS m/z 510 (MH^+)) (153B).

Example 154: N-(2,6-Dichlorobenzoyl)-4-(2,3-methylenedioxy-5-fluoro-6-methoxyphenyl)-L-phenylalanine

The title compound was prepared in a similar manner as described in Example 153. mp 198-199 °C.

Example 155: N-(2,6-Dichlorobenzoyl)-4-[4-(N-allyl-N-tert-butoxycarbonylamino)-2,6-dimethoxyphenyl]-L-phenylalanine

1) 4-(N-Allyl-N-tert-butoxycarbonylamino)-2,6-dimethoxybenzeneboronic acid and N-(2,6-dichlorobenzoyl)-O-(trifluoromethanesulfonyl)-L-tyrosine methyl ester were coupled by a similar method as described in Example 7-2) to give N-(2,6-dichlorobenzoyl)-4-[4-(N-allyl-N-tert-butoxycarbonylamino)-2,6-dimethoxyphenyl]-L-phenylalanine methyl ester.

2) The product obtained above was hydrolyzed in a similar method as described in Example 1-5) to give the title compound; mp 138-139 °C; MS m/z 629 (MH^+).

Example 156: N-(2,6-Dichlorobenzoyl)-4-(4-allylamino-2,6-dimethoxyphenyl)-L-phenylalanine

1) N-(2,6-Dichlorobenzoyl)-4-[4-[(N-allyl-N-tert-butoxycarbonylamino)-2,6-dimethoxyphenyl]-L-phenylalanine

methyl ester (1.25 g) was dissolved in CH_2Cl_2 (10 mL) and TFA (10 mL) was added and the mixture was stirred under N_2 at room temperature for 1.5 h. The mixture was evaporated and the residue was taken up with CH_2Cl_2, washed with sat. $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane/AcOEt 5:1 to 1:1) to give N-(2,6-dichlorobenzoyl)-4-(4-allylamino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (938 mg).

2) The product obtained above was hydrolyzed in a similar method as described in Example 1-5) to give the title compound. mp 262-263 °C (dec.); MS m/z 529 (MH^+).

Example 157: N-(2,6-Dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine

1) N-(2,6-Dichlorobenzoyl)-4-(4-allylamino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.93 g) was dissolved in MeCN/water (40 mL of 84:16) under N_2. Wilkinson's catalyst (79 mg) was added and the mixture was brought to boiling. After 2 h, more catalyst (170 mg) was added and the reaction continued for another 6 h. The solvent was evaporated and the residual water coevaporated with MeCN. The residue was purified by preparative TLC (silica gel; eluent: hexane/AcOEt 2:1 to 1:2) to give N-(2,6-dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester(708 mg).

2) The product obtained above was hydrolyzed in a similar method as described in Example 1-5) to give the title compound. mp 221-222 °C; MS m/z 489 (MH^+).

Example 158: N-(2,6-Dichlorobenzoyl)-4-(4-methoxycarbonylamino-2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was obtained in a similar procedure as described in Example 64 by reacting N-(2,6-

dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester with MeOCOCl instead of $MeSO_2Cl$. mp 235-236 °C; MS m/z 548 (MH^+)

Example 159: N-(2,6-Dichlorobenzoyl)-4-(4-acetylamino-2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was obtained in a similar procedure as described in Example 64 by reacting N-(2,6-dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester with MeCOCl instead of $MeSO_2Cl$. mp 243-244 °C; MS m/z 531 (MH^+).

Example 160: N-(2,6-Dichlorobenzoyl)-4-[4-(3-methylureido)-2,6-dimethoxyphenyl]-L-phenylalanine

The title compound was obtained in a similar procedure as described in Example 70 by reacting N-(2,6-dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester with MeNCO instead of MeNCS. mp 206-207 °C; MS m/z 547 (MH^+).

Example 161: N-(2,6-Dichlorobenzoyl)-4-[4-[3-(2-methylphenyl)ureido]-2,6-dimethoxyphenyl]-L-phenylalanine

The title compound was obtained in a similar procedure as described in Example 70 by reacting N-(2,6-dichlorobenzoyl)-4-(4-amino-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester with 2-methylphenyl isocyanate instead of MeNCS. mp 194-195 °C; MS m/z 622 (MH^+).

Example 162: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(3-methylthioureido)phenyl]-L-phenylalanine

The title compound was prepared in a similar manner as described in Example 70 starting from N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-4-aminophenyl)-L-

phenylalanine methyl ester. MS m/z 562 (MH^+), mp. 197-198 °C

Example 163: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(methylsulfonyl)amino]phenyl]-L-phenylalanine

The title compound was prepared in a similar manner as described in Example 64 starting from N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-4-aminophenyl)-L-phenylalanine methyl ester. MS m/z 567 (MH^+), mp. 154-155 °C

Example 164: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(dimethylamino)phenyl]-L-phenylalanine

The title compound was prepared in a similar manner as described in Example 27 starting from N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-4-aminophenyl)-L-phenylalanine methyl ester. MS m/z 517 (MH^+)

Example 165: N-(2,6-Dichlorobenzoyl)-4-(4-methylcarbamoyl-2,6-dimethoxyphenyl)-L-phenylalanine

1) 4-(1,3-Dioxolan-2-yl)-2,6-dimethoxybenzeneboronic acid was reacted with N-(2,6-dichlorobenzoyl)-O-(trifluoromethanesulfonyl)-L-tyrosine methyl ester in a similar manner as described in Example 7-2) to give N-(2,6-dichlorobenzoyl)-4-[4-(1,3-dioxolan-2-yl)-2,6-dimethoxyphenyl]-L-phenylalanine methyl ester.

2) The product obtained above was dissolved in THF (60 mL), and 5% HCl (30 mL) was added to the solution. The mixture was stirred under N_2 at room temperature for 3 h. The mixture was evaporated, and water (50 mL) was added to the residue. The mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel: eluent: hexane/AcOEt

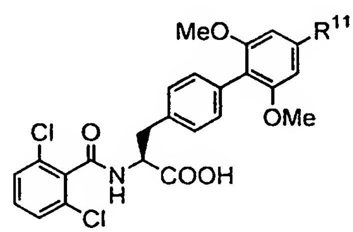
2:1 to 1:1) to give N-(2,6-dichlorobenzoyl)-4-(4-formyl-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (2.06 g).

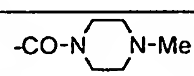
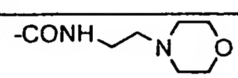
3) The product obtained above was oxidized by a similar procedure as described in Example 52-1) to give N-(2,6-dichlorobenzoyl)-4-(4-carboxy-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester.

4) The product obtained above was reacted with methylamine in a similar procedure as described in Example 53 to yield the title compound. MS m/z: 531 (MH^+); mp 251-252 °C.

The following compounds (Example 166-171) were prepared in a similar method as described in Example 53, using N-(2,6-dichlorobenzoyl)-4-(4-carboxy-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester and an appropriate amine.

TABLE 12



Example	R^{11}	m/z MH^+	mp: °C
166	$-CONMe_2$	545	219-221
167	-CONHBn	607	153-154
168	-CONH-*i*-Pr	559	261-262
169	$-CONH(CH_2)_3OH$	575	222-223
170		614	234-235
171		630	268-269

Example 172: N-(2,6-Dichlorobenzoyl)-4-(4-carboxy-2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was prepared by hydrolyzing N-(2,6-dichlorobenzoyl)-4-(4-carboxy-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester in a similar procedure as described in Example 1-5). MS m/z: 517 (MH^+); mp 277-278 °C.

Example 173: N-(2,6-Dichlorobenzoyl)-4-[4-(methanesulfonylamino)carbonyl-2,6-dimethoxyphenyl]-L-phenylalanine

The title compound was obtained in a similar procedure as described in Example 61, using N-(2,6-dichlorobenzoyl)-4-(4-carboxy-2,6-dimethoxyphenyl)-L-phenylalanine methyl ester. MS m/z: 595 (MH^+); mp 277-278 °C.

Example 174: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxy-3-methoxymethoxyphenyl)-L-phenylalanine

1) 2,6-Dimethoxy-3-methoxymethoxybenzeneboronic acid and N-(2,6-dichlorobenzoyl)-O-(trifluoromethanesulfonyl)-L-tyrosine methyl ester were coupled by a similar method as described in Example 7-2) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-methoxymethoxyphenyl)-L-phenylalanine methyl ester.

2) The product obtained above was hydrolyzed according to the procedure described in Example 7-3) to give the title compound. mp. 156-157 °C; MS m/z 534 (MH^+).

Example 175: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxy-3-hydroxyphenyl)-L-phenylalanine

1) N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxy-3-methoxymethoxyphenyl)-L-phenylalanine methyl ester (165 mg) was dissolved in MeOH (5 mL) and HCl in dioxane (4 M, 1 mL) was added to the mixture. The mixture was stirred at room

temperature for 3 h. The mixture was evaporated and the residue was taken up with water (40 mL) and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), filtered and evaporated. The residue was purified by preparative TLC (silica gel; eluent: hexane and AcOEt 3:1 to 1:1) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-hydroxyphenyl)-L-phenylalanine methyl ester (145 mg).

2) The product obtained above was hydrolyzed in a similar procedure as described in Example 1-5) to give the title compound. mp. 164-165 °C; MS m/z 490 (MH^+).

Example 176: N-[2-Chloro-4-(tert-butoxycarbonyl)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine

1) 2-Chloro-4-(tert-butoxycarbonyl)benzoic acid was coupled with 4-(2-methoxyphenyl)-L-phenylalanine methyl ester (free amine from Example 1-3)) using a similar procedure as described in Example 2-1) to give N-[2-chloro-4-(tert-butoxycarbonyl)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (0.332 g).

3) The product obtained above (19.8 mg) was hydrolyzed in a similar method as described in Example 1-5) to give the title compound (17.5 mg). MS (m/z): 508 $(M-H)^-$.

Example 177: N-[2-Chloro-4-carboxybenzoyl]-4-(2-methoxyphenyl)-L-phenylalanine

1) N-[2-Chloro-4-(tert-butoxycarbonyl)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (305 mg) was dissolved in anhydrous CH_2Cl_2 (2 mL) under N_2 and TFA (2 mL) was added. The mixture was stirred at room temperature for 2 h to give N-[2-chloro-4-carboxybenzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (315 mg).

2) The product obtained above (48.6 mg) was then hydrolyzed in a similar procedure as described in Example 1-5) to give N-[2-chloro-4-carboxybenzoyl]-4-(2-

methoxyphenyl)-L-phenylalanine (42.9 mg). MS (m/z): 452 $(M-H)^-$.

Example 178: N-[2-Chloro-4-carbamoylbenzoyl]-4-(2-methoxyphenyl)-L-phenylalanine

The title compound was prepared from N-[2-chloro-4-carboxybenzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester using a similar procedure as described in Example 60. MS (m/z): 451 $(M-H)^-$.

Example 179: N-[2-Chloro-4-[N-(methanesulfonyl)carbamoyl]-benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine

The title compound was prepared from N-[2-chloro-4-carboxybenzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester using a similar procedure as described in Example 61. MS (m/z): 529 $(M-H)^-$.

Example 180: N-[2-Chloro-5-[(trifluoromethanesulfonyl)amino]-benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine

The title compound was prepared in similar procedures as described in Examples 62, 63, 64 and 65, but replacing 2-chloro-4-nitrobenzoyl chloride with 2-chloro-5-nitrobenzoyl chloride in the coupling step of Example 62. MS (m/z): 555 $(M-H)^-$

Example 181: N-[2-Chloro-3-[(trifluoromethanesulfonyl)amino]-benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine

The title compound was obtained in similar procedures as described in Examples 62, 63, 64 and 65, but replacing 2-chloro-4-nitrobenzoyl chloride with 2-chloro-3-nitrobenzoyl chloride in the coupling step of Example 62. MS (m/z): 555 $(M-H)^-$

Example 182: N-[2,6-Dichloro-4-[(trifluoromethanesulfonyl)amino]benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine

The title compound was obtained by successively carrying out similar procedures as described in Examples 62, 63, 64 and 65, except for the use of 2,6-dichloro-4-nitrobenzoic acid (US patent 3,423,475) in the coupling step of Example 62. MS (m/z): 589 $(M-H)^-$

Example 183: N-[2-Chloro-4-[(trifluoromethanesulfonyl)amino]-benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was obtained by successively carrying out similar procedures as described in Examples 62, 63, 64 and 65, but replacing 4-(2-methoxyphenyl)-L-phenylalanine methyl ester with 4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester. MS (m/z): 585 $(M-H)^-$

Example 184: N-[2,6-Dichloro-4-[(trifluoromethanesulfonyl)amino]benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was obtained by successively carrying out similar procedures as described in Examples 62, 63, 64 and 65, but replacing 2,6-dichlorobenzoyl chloride with 2,6-dichloro-4-nitrobenzoyl chloride and replacing 4-(2-methoxyphenyl)-L-phenylalanine methyl ester with 4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester. MS (m/z): 619 $(M-H)^-$

Example 185: N-[2-Chloro-6-[(trifluoromethanesulfonyl)amino]-benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine

The title compound was obtained in similar procedures as described in Examples 62, 63, 64 and 65, except for the use of 2-amino-6-chlorobenzoic acid in the coupling step of Example 62. MS (m/z): 555 $(M-H)^-$

Example 186: N-[2-Chloro-3-[(trifluoromethanesulfonyl)amino]-benzoyl]-4-(2-methoxyphenyl)-D-phenylalanine

The title compound was obtained in similar procedures as described in Examples 62, 63, 64 and 65, but starting from 4-(2-methoxyphenyl)-D-phenylalanine methyl ester. MS (m/z): 555 $(M-H)^-$

The following compounds (Examples 187-193) were prepared in similar procedures as described in Examples 62, 63, 64 and 65, but replacing $MeSO_2Cl$ with a requisite arylsulfonyl chloride.

Example 187: N-[2-Chloro-4-[[(4-trifluoromethylphenyl)sulfonyl]amino]benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine; ESMS m/Z 655 $(M^{+}+Na)$, 633 (MH^{+}), 631 $(M-H)^-$.

Example 188: N-[2-Chloro-4-(tosylamino)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine; ESMS m/z 601 $(M^{+}+Na)$, 579 (MH^{+}), 577 $(M-H)^-$.

Example 189: N-[2-Chloro-4-[[(4-fluorophenyl)sulfonyl]amino]benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine; ESMS m/z 605 $(M^{+}+Na)$, 583 (MH^{+}), 581 $(M-H)^-$.

Example 190: N-[2-Chloro-4-[[(4-methoxyphenyl)sulfonyl]amino]-benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine; ESMS m/z 617 $(M^{+}+Na)$, 595 (MH^{+}), 593 $(M-H)^-$.

Example 191: N-[2-Chloro-4-[(2-thienylsulfonyl)amino]benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine; ESMS m/Z 593 (M^{+}+Na), 571 (MH^{+}), 569 $(M-H)^{-}$.

Example 192: N-[2-Chloro-4-[[(2-methylphenyl)sulfonyl]amino]benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine; ESMS m/z 601 (M^{+}+Na), 579 (MH^{+}), 577 $(M-H)^{-}$.

Example 193: N-[2,6-Dichloro-4-[(2-thienylsulfonyl)amino]benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine; mp. 141-142 °C. ESMS m/Z 635 (MH^{+}).

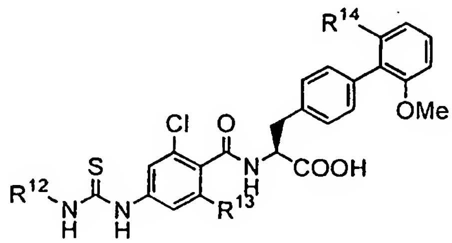
Example 194: N-[4-(3-Benzylthioureido)-2-chlorobenzoyl]-4-(2-methoxyphenyl)-L-phenylalanine

1) A solution of N-(4-amino-2-chlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine (57 mg) in DMF (1.5 mL) was added to a solution of 1, 1'-thiocarbonyldiimidazole (28 mg) in DMF (1 mL) under N_2 at 0 °C over a 2.5 h period. The mixture was then allowed to warm up slowly to room temperature and stirred for an additional 2 h. Benzylamine (21 µL) was then added and the resulting mixture stirred for 2 h at 80 °C. The mixture was concentrated, and the residue was taken up with CH_2Cl_2 and washed with 1N HCl and water. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by preparative TLC (silica gel; eluent: CH_2Cl_2/MeOH/Et_3N 100:1:1) to give a solid. The solid was taken up with CH_2Cl_2 and washed with 1N HCl, dried and evaporated to give N-[4-(3-benzylthioureido)-2-chlorobenzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester (42 mg).

2) The product obtained above was hydrolyzed in a similar procedure as described in Example 1-5) to give the title compound (26.9 mg). ESMS m/z 572 (M^{+}-1).

The following compounds (Example 195-198) were prepared in a similar manner as described in Example 70 replacing methyl isothiocyanate with appropriate isothiocyanate.

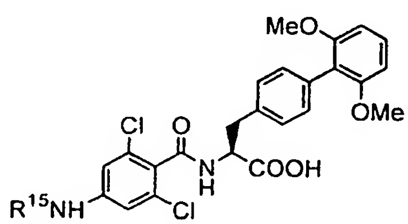
TABLE 13



Example	R^{12}	R^{13}	R^{14}	MS: m/z	mp: °C
195	i-Pr	H	H	524 $(M-H)^-$	
196	Et	H	H	510 $(M-H)^-$	155-156
197	Ph	H	H	558 $(M-H)^-$	145-146
198	Me	Cl	-OMe	546 $(M-OH)^+$	189-190

The following compounds (Examples 199-204) were prepared in a similar manner as described in Examples 64, 69 or 70.

TABLE 14



Example	R^{15}	m/z MH^+	mp, °C
199	Ac	531	227-229
200	EtOCO	561	185-187

201	MeOCO	547	147-149
202	2-MeC_6H_4NHCO	622	182-184
203	MeNHCO	546	110-112
204	H_2NCO	532	220-221

Example 205: N-(4-Ureido-2,6-dichlorobenzoyl)-4-(3-carbamoyl-2,6-dimethoxyphenyl)-L-phenylalanine

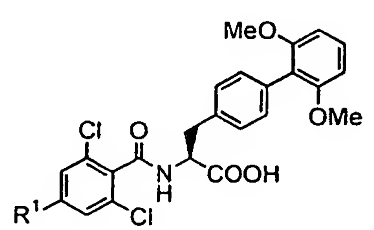
The title compound was obtained using a similar procedure as described in Example 69. ESMS m/z 575 (MH^+). mp. 217-219 °C

Example 206: N-(4-Amino-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was prepared in a similar manner as described in Example 63. ESMS m/z 489 (MH^+). mp. 221-222 °C (dec.)

The following compounds (Examples 207-208) were prepared in a similar method as described in Example 2.

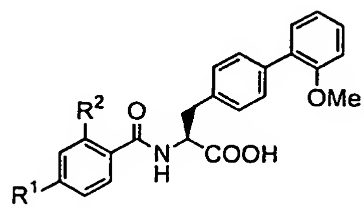
TABLE 15



Example	R^1	m/z MH^+	mp, °C
207	Br	554	184-185
208	OH	490	252-253

The following compounds (Example 209-212) were prepared in a similar manner as described in Example 1 and 2 but replacing 2,6-dichlorobenzoyl chloride and (S)-2-phenylpropionic acid with requisite benzoyl chlorides and benzoic acids.

TABLE 16



Example	R^1	R^2	m/z MH^+	mp °C
209	OH	Cl	426	
210	H_2NSO_2	H	455	
211	$MeSO_2$	Cl	488	
212	Br	Cl	490	62-63

Example 213: N-[2-(2,6-Dichlorophenyl)propionyl]-4-(2-methoxyphenyl)-L-phenylalanine

1) (2,6-Dichlorophenyl)acetic acid (2.55 g) was dissolved in anhydrous MeOH (60 mL) and HCl(gas) was passed through the mixture and the resulting solution was stirred at room temperature for 18 h. The solvent was then evaporated to give (2,6-dichlorophenyl)acetic acid methyl ester (2.7 g).

2) LDA (2 M in heptane/THF/ethyl benzene) was added to anhydrous THF (10 mL) and the mixture was cooled to -78 °C under N_2. The product obtained above (1.1 g) was added dropwise and the mixture was stirred at -78 °C for 30 min.

MeI (0.467 mL) was added and the mixture was allowed to warm up to room temperature and stirred overnight. The mixture was concentrated. The residue was taken up with AcOEt (75 mL), washed successively with 1 N HCl, water and brine. The mixture was dried ($MgSO_4$), filtered and evaporated to give 2-(2,6-dichlorophenyl)propionic acid methyl ester (1.11 g).

3) The product obtained above was dissolved in THF/MeOH/toluene (65 mL, 11:1:1) and 1 M KOH (9.18 mL) was added. The mixture was stirred at room temperature for 6h, heated to 50 °C and stirred overnight. EtOH (5 mL) was added and the mixture was stirred at 60 °C for 6 h and refluxed overnight. The mixture was concentrated and taken up with water (60 mL), acidified with 1 N HCl to pH < 2. The product was collected by filtration to give 2-(2,6-dichlorophenyl)propionic acid (0.84 g).

4) The product obtained above was coupled with 4-(2-methoxyphenyl)-L-phenylalanine methyl ester by a similar procedure as described in Example 2 and hydrolyzed with LiOH to give the title compound. ESMS m/z 472 (MH^+). mp. 109-110 °C.

The following compounds (Examples 214-217) were prepared in a similar procedure as described in Example 4.

Example 214: N-(2,6-Dichlorobenzoyl)-4-(2-formyl-3-thienyl)-L-phenylalanine; ESMS m/z 470 (M^++Na), 448 (MH^+), 446 $(M-H)^-$.

Example 215: N-(2,6-Dichlorobenzoyl)-4-(5-acetyl-2-thienyl)-L-phenylalanine: mp. 194-195 °C. ESMS m/z 484 (M^++Na), 462 (MH^+), 460 $(M-H)^-$.

Example 216: N-(2,6-Dichlorobenzoyl)-4-[(3,5-dimethyl-4-isoxazolyl)-2,6-dimethoxyphenyl]-L-phenylalanine:ESMS m/z 433 (MH^+); mp. 118.7 °C.

Example 217: N-(2,6-Dichlorobenzoyl)-4-(4-pyridyl)-L-phenylalanine: ESMS m/z 415 (MH^+).

Example 218: N-(2,6-Dichlorobenzoyl)-4-(2-hydroxymethyl-3-thienyl)-L-phenylalanine

The title compound was prepared by $NaBH_4$ reduction of N-(2,6-Dichlorobenzoyl)-4-(2-formyl-3-thienyl)-L-phenylalanine methyl ester followed by hydrolysis as described in Example 50. ESMS m/z 472 (M^++Na), 448 $(M-H)^-$.

Example 219: N-(2,6-Dichlorobenzoyl)-4-(2-cyano-3-thienyl)-L-phenylalanine

1) A mixture of N-(2,6-dichlorobenzoyl)-O-(trifluoromethane sulfonyl)-L-tyrosine methyl ester (361 mg), trimethyl(2-cyano-3-thienyl)tin (393 mg), $Pd(PPh_3)_4$ (42 mg) and LiCl (93 mg) in dioxane (8 mL) was stirred at 100 °C under N_2 for 38 h. The mixture was diluted with AcOEt and treated with 10% NH_4Cl aqueous solution (6 mL). After stirring at room temperature for 1 h, the mixture was filtered through Celite and washed with AcOEt. The combined organic layers were washed successively with water and brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by silica gel chromatography to afford N-(2,6-dichlorobenzoyl)-4-(2-cyano-3-thienyl)-L-phenylalanine methyl ester (126 mg). ESMS m/z 481 (M^++Na), 459 (MH^+), 457 $(M-H)^-$.

2) The product obtained above was hydrolyzed with LiOH as described in Example 1-5) to afford N-(2,6-dichlorobenzoyl)-4-(2-cyano-3-thienyl)-L-phenylalanine (110 mg); ESMS m/z 467 (M^++Na), 445 (MH^+), 443 $(M-H)^-$.

The following compounds (Example 220-226) were prepared in a similar manner as described in Example 32.

Example 220: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(3-thienylmethoxy)phenyl]-L-phenylalanine; ESMS m/z 584 $(M-H)^-$.

Example 221: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(2,6-dichlorophenyl)methoxy]phenyl]-L-phenylalanine; ESMS m/z 672 $(M^+ +Na)$, 648 $(M-H)^-$.

Example 222: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(2-hydroxyethoxy)phenyl]-L-phenylalanine; ESMS m/z 556 $(M^+ +Na)$, 534 (MH^+), 532 $(M-H)^-$.

Example 223: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[2-(N,N-dimethylamino)ethoxy]phenyl]-L-phenylalanine: ESMS m/z 561 (MH^+).

Example 224: N-(2,6-Dichlorobenzoyl)-4-(3-i-propoxyphenyl)-L-phenylalanine; ESMS m/z 494 $(M^+ +Na)$, 472 (MH^+), 470 $(M-H)^-$.

Example 225: N-(2,6-Dichlorobenzoyl)-4-(2-i-propoxyphenyl)-L-phenylalanine; ESMS m/z 494 $(M^+ +Na)$, 472 (MH^+), 470 $(M-H)^-$.

Example 226: N-(2,6-Dichlorobenzoyl)-4-(2-i-propyloxy-6-methoxyphenyl)-L-phenylalanine; ESMS m/z 524 $(M^+ +Na)$, 500 $(M-H)^-$.

Example 227: N-(2,6-Dichlorobenzoyl)-4-[6-methoxy-2-(2-hydroxyethoxy)phenyl]-L-phenylalanine

1) 6-Methoxy-2-methoxymethoxybenzeneboronic acid (1.92g) was coupled with N-(2,6-dichlorobenzoyl)-O-(trifluoromethanesulfonyl)-L-tyrosine ethyl ester in a

similar procedure as described in Example 5-3) to afford N-(2,6-dichlorobenzoyl)-4-(6-methoxy-2-methoxymethoxyphenyl)-L-phenylalanine ethyl ester (0.942 mg). ESMS m/Z 532 (MH^+), 530 $(M-H)^-$.

2) To a solution of N-(2,6-dichlorobenzoyl)-4-(6-methoxy-2-methoxymethoxyphenyl)-L-phenylalanine ethyl ester (938 mg) in EtOH (25 mL) was added HCl (4 N in dioxane, 5 mL), and then the mixture was stirred under N_2 for 4 h at room temperature. The mixture was diluted with AcOEt, washed with H_2O and brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel; eluent: AcOEt/hexane 1 : 2) to afford N-(2,6-dichlorobenzoyl)-4-(6-methoxy-2-hydoxyphenyl)-L-phenylalanine ethyl ester (795mg). ESMS m/Z 488 (MH^+), 486 $(M-H)^-$.

3) A mixture of the product obtained above(256 mg), 2-bromoethyl acetate (271 mg) and K_2CO_3 (217 mg) in DMF (5 mL) was stirred at 60 °C under N_2 for 15 h. The mixture was diluted with AcOEt, washed with H_2O and brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel; eluent: AcOEt/hexane 1:5-1:3) to afford N-(2,6-dichlorobenzoyl)-4-[6-methoxy-2-(2-acetoxyethoxy)phenyl]-L-phenylalanine ethyl ester (203 mg). ESMS m/Z 574 (MH^+), 572$(M-H)^-$.

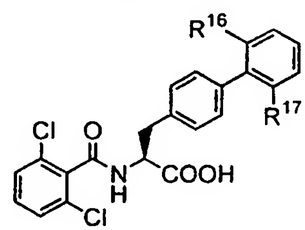
4) The product obtained above (196 mg) was hydrolyzed with LiOH (29mg) as described in Example 1-5). The crude material was crystallized from CH_2Cl_2/AcOEt/hexane to afford the title compound (145 mg). mp 158-159 °C; ESMS m/Z 526 (M^++Na), 504 (MH^+), 502 $(M-H)^-$.

Example 228: N-(2,6-Dichlorobenzoyl)-4-[6-methoxy-2-(2-fluoroethoxy)phenyl]-L-phenylalanine.

The title compound was prepared in a similar method as described in Example 227 but replacing 2-bromoethylacetate with 2-fluoroethyl bromide. mp 206 -207 °C; ESMS m/Z 506 (MH^+).

The following compounds (Examples 229-232) were prepared in a similar procedure as described in Example 227 using requisite benzeneboronic acid.

TABLE 17



Example	R^{16}	R^{17}	m/z (MH^+)	mp (°C)
229	$-OCH_2CH_2OH$	$-OCH_2CH_2OH$	534	124-125
230	$-OCH_2CF_3$	$-OCH_2CF_3$	610	93-94
231	$-OCH_2CN$	$-OCH_2CN$	524	175-176
232	$-OCH_2CH_2N(CH_3)_2$	-OH	517	168-169

The following compounds (Examples 233-241) were obtained in a similar manner as described in Example 228 using requisite benzeneboronic acid.

Example 233: N-(2,6-Dichlorobenzoyl)-4-[2,3-methylenedioxy-6-(2-methoxyethoxy)phenyl]-L-phenylalanine. mp 167-168 °C; ESMS m/Z 532 (MH^+).

Example 234: N-(2,6-Dichlorobenzoyl)-4-[2,3-methylenedioxy-6-[2-(N,N-dimethylamino)ethoxy]phenyl]-L-phenylalanine; ESMS m/z 545 (MH^+), 543 $(M-H)^-$.

Example 235: N-(2,6-Dichlorobenzoyl)-4-[2,3-methylenedioxy-6-(methoxymethoxy)phenyl]-L-phenylalanine; ESMS m/z 518 (MH^+), 516 $(M-H)^-$.

Example 236: N-(2,6-Dichlorobenzoyl)-4-(2,3-methylenedioxy-6-hydroxyphenyl)-L-phenylalanine; ESMS m/z 474 (MH^+).

Example 237: N-(2,6-Dichlorobenzoyl)-4-(2,3-methylenedioxy-6-ethoxyphenyl)-L-phenylalanine; ESMS m/z 502 (MH^+).

Example 238: N-(2,6-Dichlorobenzoyl)-4-[2,3-methylenedioxy-6-(2-hydroxyethoxy)phenyl]-L-phenylalanine; ESMS m/z 518 (MH^+), 516 $(M-H)^-$.

Example 239: N-(2,6-Dichlorobenzoyl)-4-[2,3-methylenedioxy-6-(cyanomethoxy)phenyl]-L-phenylalanine; ESMS m/z 513 (MH^+).

Example 240: N-(2,6-Dichlorobenzoyl)-4-(2,3-methylenedioxy-6-methoxyphenyl)-L-phenylalanine; ESMS m/z 488 (MH^+).

Example 241: N-(2,6-Dichlorobenzoyl)-4-(2,3-ethylenedioxy-6-methoxyphenyl)-L-phenylalanine: ESMS m/z 502(MH^+). mp. 218 °C.

Example 242: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(methylamino)methyl]phenyl]-L-phenylalanine (TR-14454)

1) A mixture of 2,6-dimethoxy-4-[(t-butyldiphenylsilyl-oxy)methyl]benzeneboronic acid (5.2 g), N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester (1.71 g), $Pd(PPh_3)_4$ (0.44 g) and K_2CO_3 (1.59 g) in DME/H_2O (20 mL/ 0.5 mL) was heated at 80 °C for 24 h under N_2. The mixture was worked up and purified in a similar procedure as described in Example 8-3) to yield 2.9 g of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(t-

butyldiphenylsilyloxy)methyl]phenyl]-L-phenylalanine ethyl ester. ESMS: m/z 770 (MH^+).

2) To an ice-cold solution of the product obtained above (2.9 g) in THF (10 mL) was added tetrabutylammonium fluoride (4.45 mL, 1 M in THF) under N_2 and the mixture was stirred for 2 h. THF was evaporated and the residue was purified by preparative TLC (eluent: hexane-hexane/EtOAc 50%) to yield 1.86 g of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(hydroxymethyl)phenyl]-L-phenylalanine ethyl ester. ESMS: m/z 532 (MH^+).

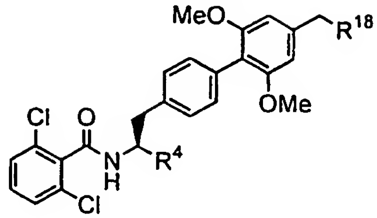
3) A mixture of the product obtained above (1.8 g), CBr_4 (2.25 g), Ph_3P (1.78 g) in CH_2Cl_2 (20 mL) was stirred at 0°C overnight. The solvent was evaporated and the residue was purified by column chromatography (silica gel; eluent: hexane-hexane/EtOAc 10%) to give 0.9 g of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(bromomethyl)phenyl]-L-phenylalanine ethyl ester. ESMS: m/z 596 (MH^+).

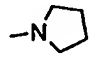
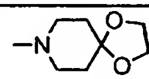
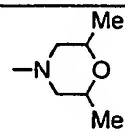
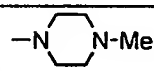
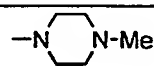
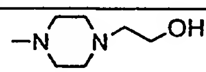
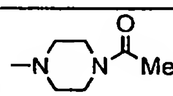
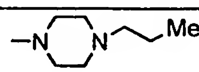
4) A mixture of the product obtained above (0.15 g) and $MeNH_2$ (2M THF, 0.8 mL) in CH_2Cl_2 (3 mL) was stirred at room temperature for 4 h. The crude mixture was purified by preparative TLC (silica gel; eluent: CH_2Cl_2/EtOH 9.5/5 with few drops of NH_4OH) to yield 45 mg of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(methylamino)methyl]phenyl]-L-phenylalanine ethyl ester. ESMS: 545 (MH^+).

5) The product obtained above (0.093 g) was hydrolyzed with LiOH (2N, 0.175 mL) as described in Example 1-5) to give 75 mg of the title compound; mp. 274 °C. ESMS: 517 m/z (MH^+).

The following compounds (Examples 243-252) were prepared in an analogous manner as described in Example 242 by replacing $MeNH_2$ with the requisite amines.

TABLE 18



Example	R^4	R^{18}	Physical properties
243	-COOH		MS: m/z 557 (MH^+)
244	-COOH		MS: m/z 629 (MH^+)
245	-COOH		MS: m/z 601 (MH^+)
246	-COOH	$-NH(CH_2)_2OH$	MS: m/z 547 (MH^+)
247	-COOH	$-N(Me)CH_2CH_2N(Me)_2$	MS: m/z 588 (MH^+)
248	-COOH		MS: m/z 586 (MH^+)
249	-COOEt		MS: 614 (MH^+) mp. 148-150.5 °C 2HCl salt: mp. 235 °C (dec.)
250	-COOH		MS: m/z 616 (MH^+)
251	-COOH		MS: m/z 614 (MH^+)
252	-COOH		MS: m/z 614 (MH^+)

Example 253: N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl)phenyl]-L-phenylalanine

1) A mixture of 2,6-dimethoxy-4-(thiomorpholinomethyl)-benzeneboronic acid (1.1 g), N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester (0.71 g), $Pd(PPh_3)_4$ (1.0 g) and K_2CO_3 (1.00 g) in DME/H_2O (10 mL/ 0.5 mL) was heated

at 80 °C for 6 h under N_2. The mixture was worked up and purified according to the procedure described in Example 8-3) to yield 0.15 g of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl)phenyl]-L-phenylalanine ethyl ester. mp. 86-89 °C. ESMS: m/z 616 (MH^+). HCl salt: mp. 204-205 °C.

2) The product obtained above (0.15 g) was hydrolyzed with LiOH as described in Example 1-5) to give 120 mg of the title compound. ESMS: m/z 588 (MH^+).

The following compounds (Example 254-261) were prepared in a similar manner as described in Example 242 or 253 from requisite starting materials.

Example 254: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(diethylamino)methyl]phenyl]-L-phenylalanine; ESMS: m/z 559 (MH^+)

Example 255: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(N,N-dimethylamino)methyl]phenyl]-L-phenylalanine; ESMS: m/z 531 (MH^+)

Example 256: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(piperidinomethyl)phenyl]-L-phenylalanine; ESMS: m/z 571 (MH^+)

Example 257: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl)phenyl]-L-phenylalanine; ESMS: m/z 573 (MH^+)

Example 258: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-benzyl-1-piperazinyl)methyl]phenyl]-L-phenylalanine; ESMS: m/z 662 (MH^+)

Example 259: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(N,N-dimethylamino)methyl]phenyl]-L-phenylalanine ethyl ester hydrochloride; ESMS: m/z 560 (MH^+); mp. 146.5 °C.

Example 260: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(piperidinomethyl)phenyl]-L-phenylalanine ethyl ester hydrochloride; ESMS: m/z 600 (MH^+); mp. 205.5 °C.

Example 261: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl)phenyl]-L-phenylalanine ethyl ester hydrochloride; ESMS: m/z 601 (MH^+); mp. 177.5 °C.

Example 262: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(1-piperazinyl)methyl]phenyl]-L-phenylalanine

1) N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-tert-butoxycarbonyl-1-piperazinyl)methyl]phenyl]-L-phenylalanine ethyl ester was obtained in a similar method as described in Example 253 by replacing 2,6-dimethoxy-4-(thiomorpholinomethyl)benzeneboronic acid with 2,6-dimethoxy-4-[(4-tert-butoxycarbonyl-1-piperazinyl)methyl]benzeneboronic acid.

2) A solution of the product obtained above (0.09 g) in CH_2Cl_2 /TFA (5 /3 mL) was stirred at room temperature for 3 h. The mixture was evaporated and the residue was partitioned between EtOAc and satd. $NaHCO_3$. The EtOAc layer was washed with water, dried and evaporated to yield 70 mg of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(1-piperazinyl)methyl]phenyl]-L-phenylalanine ethyl ester. ESMS: m/z 600 (MH^+).

3) The product obtained above was hydrolyzed in a similar method as described in Example 1-5) to give 50 mg the title compound. ESMS: m/z 572 (MH^+).

Example 263: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl)phenyl]-L-phenylalanine S-oxide (263B) and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl)phenyl]-L-phenylalanine S,S- dioxide (263A).

1) To a solution of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl)phenyl]-L-phenylalanine ethyl ester (0.1 g) in CH_2Cl_2 (3 mL) at -10 °C under N_2 was added mCPBA (40 mg) and the mixture was stirred for 2 h. The mixture was diluted with CH_2Cl_2, washed with satd. $NaHCO_3$ and brine, dried, evaporated and purified by a preparative TLC to give N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl)phenyl]-L-phenylalanine ethyl ester S-oxide (49 mg; ESMS: M/Z 633 (MH^+)) and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl)phenyl]-L-phenylalanine ethyl ester S,S-dioxide (10 mg; ESMS: m/z 649 (MH^+)).

2) The two products obtained above were separately hydrolyzed in a similar method as described in Example 1-5) to give N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl)phenyl]-L-phenylalanine S-oxide (17 mg; mp. 162.8 °C. ESMS: m/z 605 (MH^+)) and N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(thiomorpholinomethyl)phenyl]-L-phenylalanine S,S-dioxide(7 mg; mp. 230 °C (dec.) ESMS: m/z 621 (MH^+)).

Example 264: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-[2-(4-methyl-1-piperazinyl)ethyl]phenyl]-L-phenylalanine.

1) 2,6-Dimethoxy-4-(2-hydroxyethyl)benzeneboronic acid was coupled with N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester according to the procedure described in Example 8-3) to yield 1.3 g of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(2-

hydroxyethyl)phenyl]-L-phenylalanine ethyl ester. ESMS: m/z 546 (MH^+).

2) The product obtained above (1.25 g) was dissolved in CH_2Cl_2 and Ph_3P (907 mg) was added, then the solution was cooled to 0 °C. CBr_4 (1.14g) was added to the mixture and the mixture was stirred at 0 °C for 2 h. The mixture was partitioned between H_2O/EtOAc (20 mL each). The organic layer was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel; eluent: EtOAc/hexane 3/7) to give N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(2-bromoethyl)phenyl]-L-phenylalanine ethyl ester. (1.1 g). ESMS: m/z 610 (MH^+).

3) The product obtained above (200 mg) was dissolved in CH_2Cl_2 (3 mL) and the N-methylpiperazine (0.11 mL) was added. The mixture was stirred at room temperature for 40 h and evaporated. The residue was purified by column chromatography (silica gel; eluent: CH_2Cl_2/EtOH 96/4) to give N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[2-(4-methyl-1-piperazinyl)ethyl]phenyl]-L-phenylalanine ethyl ester (113 mg). ESMS: m/z 628 (MH^+).

4) The product obtained above was hydrolyzed with LiOH as described in Example 1-5) to give N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[2-(4-methyl-1-piperazinyl)ethyl]phenyl]-L-phenylalanine. mp. 178.9 °C. ESMS: *m/z* 600 (MH^+).

Example 265: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(2-piperidinoethyl)phenyl]-L-phenylalanine

The title compound was synthesized in a similar manner as described in Example 264 replacing N-methylpiperazine by piperidine. mp. 194.9 °C. ESMS *m/z*: 585 (MH^+).

Example 266: N-(2,6-Dichlorothiobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine

1) A mixture of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.25g) and Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disufide; 0.21 g) in xylene (10 mL) was refluxed overnight. The mixture was cooled to about 50 °C and water (15 mL) was added and refluxed for 2 h. The mixture was stirred at room temperature overnight and evaporated. The residue was partitioned between EtOAc and water. The EtOAc layer was washed with water, dried and evaporated to yield 0.25 g of N-(2,6-dichlorothiobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester. ESMS: m/z 504 (MH^+).

2) The product obtained above was hydrolyzed with LiOH as described in Example 1-5). The crude product was purified by column chromatography (silica gel; eluent CH_2Cl_2/MeOH 95:5 to CH_2Cl_2/MeOH/AcOH 95:5:0.1) to give 25 mg of the title compound. mp. 180.4 °C. ESMS: m/z 490 (MH^+).

Example 267: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine N-(methylsulfonyl)amide

1) To a solution of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine (0.1 g) in THF (5 mL) at 0 °C under N_2 was added oxalyl chloride (0.055 mL) followed by a drop of DMF. The solution was stirred at 0 °C for 2h followed by stirring at room temperature for 2 h. THF was evaporated and fresh THF (5 mL) was added and the solution was evaporated again. This process was repeated one more time and the residue was dried under vacuum to yield N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanyl chloride.

2) To a solution of the product obtained above in THF (10 mL) was added $MeSO_2NH_2$ (0.0292 g) followed by DBU

(0.035 mL). The mixture was stirred at room temperature for 4 h and heated under reflux for 2 h. The mixture was evaporated and the residue was purified by column chromatography (silica gel; eluent: CH_2Cl_2 to CH_2Cl_2/MeOH 3%) and recrystallization from CH_2Cl_2/Et_2O to give 25 mg of the title compound. ESMS: m/z 551 (MH^+).

Example 268: N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine N-hydroxyamide.

$NaHCO_3$ (0.21 g) was added to a solution of NH_2OH HCl (0.14 g) in THF/water (5 mL each) at 0 °C and the mixture was stirred for 1/2 h. A solution of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanyl chloride (0.1 g) in THF (5 mL) was added to the mixture at 0 °C and the mixture was stirred overnight at room temperature. The mixture was partitioned between EtOAc and water. The EtOAc layer was washed successively with 1 N HCl and brine, dried and evaporated. The residue was purified by preparative TLC (silica gel; eluent: CH_2Cl_2/MeOH 8%) to yield 27 mg of the title compound. ESMS: m/z 489 (MH^+).

Example 269: N-(2,6-Dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine N-hydroxyamide.

1) To a solution of N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine (0.098 g) and tert-butylhydroxylamine (0.047 g) in CH_2Cl_2 (5 mL) was added BOP reagent (0.17 g) followed by DIEA (0.1 mL) and the mixture was stirred overnight at room temperature. The mixture was evaporated and the residue was dissolved in EtOAc (30 mL). The EtOAc solution was successively washed with 1 N HCl, satd. $NaHCO_3$, satd. LiCl, dried ($MgSO_4$), and concentrated. The residue was purified by preparative TLC (silica gel; eluent: hexane/EtOAc/CH_2Cl_2 6/1/1) and recrystallization

from CH_2Cl_2/hexane to give 74 mg of N-(2,6-dichlorobenzoyl)-4-(2-methoxyphenyl)-L-phenylalanine N-(tert-butyl)-N-hydroxyamide. ESMS: m/z 515 (MH^+).

2) A solution of the product obtained above (0.030 g) in CH_2Cl_2/TFA (3 mL each) was stirred for 72 h at room temperature. The mixture was evaporated and the residue was purified by column chromatography (silica gel; eluent: CH_2Cl_2 to CH_2Cl_2/MeOH 5%) to give 10 mg of the title compound. ESMS: m/z 459 (MH^+).

Example 270: (1S)-N-(2,6-Dichlorobenzoyl)-2-[4-(2,6-dimethoxyphenyl)phenyl]-1-(1H-tetrazol-5-yl)ethylamine.

The title compound was prepared by following the procedure described in the J. Med. Chem., 41, 1513-1518, 1998.

1) A solution of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine (0.17 g), HOBT (0.0.08 g), DIEA (0.19 mL) and 2-cyanoethylamine (0.03 mL) in DMF (5 mL) was stirred at room temperature under N_2. EDC (0.14 g) was added after 10 min and the mixture was stirred at room temperature under N_2. The mixture was diluted with water and extracted with EtOAc. The extract was washed successively with water, 1 N HCl, satd. $NaHCO_3$ and brine, dried and evaporated to give 0.17 g of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine N-(2-cyanoethyl)amide. ESMS : m/z 526 (MH^+).

2) Ph_3P (0.21 g) was added to a solution of the product obtained above (0.17 g) in MeCN (10 mL). The mixture was cooled to 0 °C, and DIAD (0.16 mL) and $TMSN_3$ (0.11 mL) was added. The mixture was allowed to warm to room temperature, heated to 40 °C for 1 h, cooled to room temperature and stirred overnight. The mixture was partitioned between EtOAc and water. The organic layer was washed with satd. $NaHCO_3$ followed by brine, dried ($MgSO_4$), filtered and

evaporated. The residue was purified by column chromatography (silica gel; eluent: EtOAc/hexane 1/1) to yield 0.076 mg of (1S)-N-(2,6-dichlorobenzoyl)-2-[4-(2,6-dimethoxyphenyl)phenyl]-1-[1-(2-cyanoethyl)-1H-tetrazol-5-yl]ethylamine. ESMS: m/z 551 (MH^+).

3) To a solution of the product obtained above (0.073 g) in $CHCl_3$ (5 mL) was added DBU (0.059 mL) and the mixture was stirred for 48 h at room temperature under N_2. The mixture was diluted with EtOAc, washed with 1N HCl and brine, dried and evaporated to yield 0.067 g of the title compound. ESMS: m/z 498 (MH^+).

The following compounds (Example 271-274) were prepared in a similar procedure as described in Example 270-1).

Example 271: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine 2-(dimethylamino)ethyl ester; ESMS: m/z 582 (MH^+).

Example 272: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine 2-pyridylmethyl ester; ESMS: m/z 582 (MH^+).

Example 273: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine 3-pyridylmethyl ester; ESMS: m/z 582 (MH^+).

Example 274: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine 4-pyridylmethyl ester; ESMS: m/z 582 (MH^+).

Example 275: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine i-propyl ester.

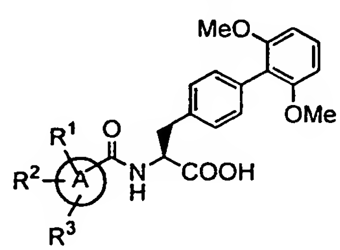
HCl gas was bubbled into a solution of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine (0.15 g) in THF/2-propanol (2/5 mL) for 15 min and the solution was stirred overnight at room temperature. The mixture was saturated with HCl gas, allowed to stand overnight at room temperature, and evaporated. The residue was partitioned between EtOAc and water. The EtOAc layer was washed with water, dried, evaporated and the residue was purified by column chromatography (eluent: EtOAc/hexane 1/1) and triturated with hexane/Et_2O (5/0.5) to give 0.1 g of the title compound. ESMS: m/z 516 (MH^+).

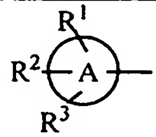
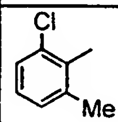
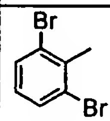
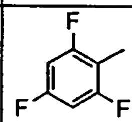
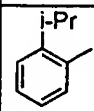
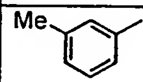
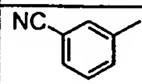
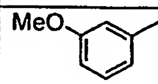
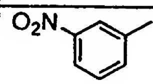
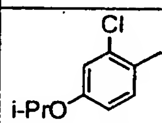
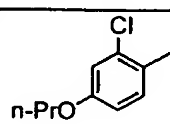
Example 276: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine cyclohexyl ester

The title compound was prepared in an analogous manner to Example 275 by replacing 2-propanol with cyclohexanol. ESMS: m/z 556 (MH^+).

The following compounds (Examples 277-286) were prepared in a similar method as described in Example 1 or Example 2, replacing 2,6-dichlorobenzoic acid or 2,6-benzoyl chloride with an appropriate substituted benzoic acid or acid chloride thereof.

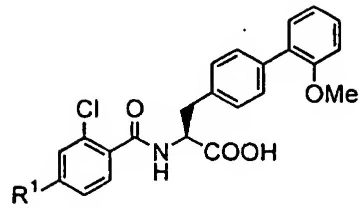
TABLE 19

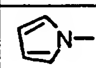
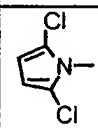
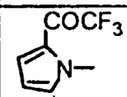
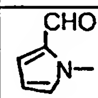


Example		m/z MH^+
277		455
278		564 $(M-H)^-$
279		460
280		448
281		420
282		431
283		438
284		451
285		498
286		498

The following compounds (Examples 287-290) were prepared in an analogous manner as described in Example 2 by replacing (S)-2-phenylpropionic acid with properly substituted 2-chlorobenzoic acids.

TABLE 20



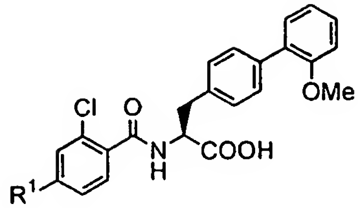
Example	R^1	m/z
287		475 (MH^+)
288		543 (MH^+)
289		569 $(M-H)^-$
290		501 $(M-H)^-$

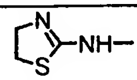
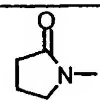
Example 291: N-[2-Chloro-4-(2-hydroxymethyl-1-pyrrolyl)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine.

The title compound was obtained from N-[2-chloro-4-(2-formyl-1-pyrrolyl)benzoyl]-4-(2-methoxyphenyl)-L-phenylalanine methyl ester by reduction with $NaBH_4$ followed by saponification with LiOH as described in Example 50. MS m/z: 503 $(M-H)^-$.

The following compounds (Example 292-293) were prepared in a similar method as described in Example 2.

TABLE 21



Example	R^1	m/z
292		510
293		493

Example 294: N-(2,6-Dichlorobenzoyl)-3-[5-(2,6-dimethoxyphenyl)-2-thienyl]-L-alanine

1) N-(9-Fluorenylmethoxycarbonyl)-3-(5-bromo-2-thienyl)-L-alanine (813 mg) was dissolved in EtOH (15 mL) and HCl (gas) was bubbled through the solution for 5 min at 0°C. The mixture was warmed to 50 °C and stirred for 1 h. After cooling to room temperature the solvent was evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane to hexane/EtOAc 1:1) provided N-(9-fluorenylmethoxycarbonyl)-3-(5-bromo-2-thienyl)-L-alanine ethyl ester (767 mg): ESMS: m/z 500 MH^+.

2) Piperidine (1 mL) was added to a solution the product obtained above (758 mg) in CH_2Cl_2 (10 mL). The mixture was warmed to 45°C, stirred for 2 h, and evaporated. The residue was dissolved in CH_2Cl_2 (10 mL) and Et_3N (1.1 mL). To this solution 2,6-dichlorobenzoyl chloride (240 µL) was added and the mixture was stirred at room temperature overnight. 1 N HCl (20 mL) was added and the mixture was extracted with EtOAc. The extract was dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane to hexane/EtOAc

1:1) to give N-(2,6-dichlorobenzoyl)-3-(5-bromo-2-thienyl)-L-alanine ethyl ester (650 mg): ESMS: m/z 450 (MH^+).

3) The title compound was prepared from the product obtained above by following procedures described in Example 7-2) and 3). ESMS: m/z 480 (MH^+). mp. 134°C (dec.)

Example 295: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-homophenylalanine.

The title compound was prepared in a similar manner as described in Example 5. ESMS: m/z 488 (MH^+). mp. 105-107 °C

Example 296: N-(2,6-Dichlorobenzoyl)-3-ethyl-4-(2-methoxyphenyl)-L-phenylalanine.

1) To a solution of N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethyl)-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (0.08 g) in CH_3CN (3 mL) at 0 °C was added Et_3SiH (0.075 mL) followed by $BF_3.Et_2O$ (0.0197 mL). The mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched with CH_3OH/H_2O and the mixture was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by preparative TLC (silica gel; eluent: EtOAc/hexane 1/2) to give 39 mg of N-(2,6-dichlorobenzoyl)-3-ethyl-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester. ESMS: m/z 500 (MH^+).

2) The product obtained above was hydrolyzed with LiOH as described in Example 1-5) to give 30 mg of the title compound. mp. 105-107 °C. ESMS: m/z 472 (MH^+).

Example 297: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-3-acetylamino-L-phenylalanine.

1) N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-3-nitro-L-phenylalanine ethyl ester was prepared in a similar manner as described in Example 1 by replacing N-(tert-

butoxycarbonyl)-L-tyrosine ethyl ester with N-tert-butoxycarbonyl-3-nitro-L-tyrosine ethyl ester.

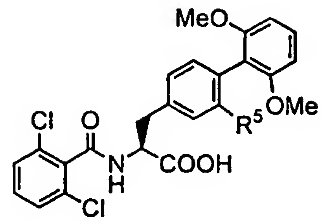
2) The product obtained above (1.07 g) was dissolved in MeOH (15 mL) under N_2. Raney-Ni (100 mg) was added and H_2 gas was bubbled through the mixture for 15 min. Stirring under H_2 was continued for 6 h. The mixture was filtered through Celite and washed with MeOH. The filtrate was evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane to hexane/EtOAc 1:1) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-3-amino-L-phenylalanine ethyl ester (845 mg): ESMS: m/z 503 MH^+.

3) The product obtained above (119 mg) was dissolved in CH_2Cl_2 (1 mL) and pyridine (57 µL). To this solution was added acetic anhydride (45 µL) and the mixture was stirred at room temperature for 18 h. The mixture was evaporated and the residue was purified by column chromatography (silica gel; eluent: hexane to EtOAc) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-3-acetylamino-L-phenylalanine ethyl ester (127 mg): ESMS: m/z 545 (MH^+).

4) The product obtained above (126 mg) was hydrolyzed with LiOH as described in Example 1-5) to give the title compound (98 mg): mp. 142-144 °C; ESMS: m/z 531 (MH^+).

The following compounds (Examples 298-300) were prepared in a similar method as described in Example 297.

TABLE 22



Example	R^5	m/z MH^+	mp, °C
298	CH_3SO_2NH	567	118-120
299	EtOCONH	561	216-217

Example 300: N-(2,6-dichlorobenzoyl)-3-(2-oxo-1-pyrrolidinyl)-4-(2,6-dimethoxyphenyl)-L-phenylalaine

1) To a solution of N-(2,6-dichlorobenzoyl)-3-nitro-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (1.07 g) in MeOH (15 mL) was added Raney-Ni (100 mg) and H_2 gas was bubbled through the mixture for 15 min. The mixture was filtered through Celite and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel; eluent: hexane to hexane/EtOAc 1:1) to give N-(2,6-dichlorobenzoyl)-3-amino-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (845 mg). ESMS: m/z 503 (MH^+).

2) To a solution of the product obtained above (122 mg) in CH_2Cl_2 (1mL) and pyridine (78 µL) was added 4-chlorobutyryl chloride (54 µL). The mixture was stirred at room temperature for 12 hours and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel; eluent: hexane to EtOAc) to give N-(2,6-dichlorobenzoyl)-3-(4-chlorobutyrylamino)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (56 mg). ESMS: m/z 607 (MH^+).

3) To a solution of the product obtained above (56 mg) in DMF (1 mL) was added NaH (11 mg. 60% in oil), and the

mixture was stirred at room temperature for 30 min. 1N HCl was added to the mixture and the mixture was extracted with EtOAc. The extract was dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography (silica gel; eluent: CH_2Cl_2 to $MeOH/CH_2Cl_2$ 10%) to give the title compound (23 mg). ESMS: m/z 557 (MH^+).

The following compounds (Examples 301-302) were prepared in a similar manner as described in Example 2 by replacing 2-phenylpropionic acid with the requisite benzoic acid and replacing 4-(2-methoxyphenyl)-L-phenylalanine methyl ester hydrochloride with 4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester hydrochloride .

Example 301: N-(2,6-Dichloro-4-phenylbenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine: ESMS: m/z 550 (MH^+); mp. 215 °C.

Example 302: N-[2,6-Dichloro-4-(1-methyl-2-pyrrolyl)benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine. ESMS: m/z 553 (MH^+). mp. 199 °C.

Example 303: N-[4-(2-Pyrrolyl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

1) N-(4-Bromo-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.410 g) was coupled with 1-tert-butoxycarbonyl-2-pyrroleboronic acid (0.930 g) in THF (10 mL) as described in Example 7-2) to give 0.435 g of N-[4-(1-tert-butoxycarbonyl-2-pyrrolyl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester. ESMS: m/z 653 (MH^+).

2) The compound obtained above was treated with TFA as described in Example 1-3) to give N-[4-(2-pyrrolyl)-2,6-

dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.198 g). ESMS: m/z 553 (MH^+).

3) The product obtained above (0.170 g) was hydrolyzed with LiOH as described in Example 1-5) to yield the title compound (0.127 g). ESMS: m/z 539 (MH^+). mp. 250 °C.

Example 304: N-[4-(5-Pyrazolyl)-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

1) N-(4-Bromo-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.240 g) was coupled with 1-[[2-(trimethylsilyl)ethoxy]methyl]-5-pyrazoleboronic acid (0.343 g) in THF (10 mL) as described in Example 7-2) to give N-[4-[1-[[2-(trimethylsilyl)ethoxy]methyl]-5-pyrazolyl]-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.277 g). ESMS: m/z 684 (MH^+) and 682 $(M-H)^-$.

2) To a solution of the product obtained above (0.277 g) in MeOH (10 mL) was added conc. HCl (0.20 mL) and a second aliquot of conc. HCl (0.20 mL) after 3 h. After stirring overnight at room temperature, the mixture was concentrated. The residue was dissolved in EtOAc, washed with $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by preparative TLC (silica gel; eluent: hexane to hexane/EtOAc 1:1) to yield N-[4-(5-pyrazolyl)-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.148 g). ESMS: m/z 554 (MH^+).

3) The product obtained above was hydrolyzed in a similar manner as described in Example 1-5) to give the title compound (0.133 g). ESMS: m/z 540 (MH^+) and 652 (M^- +TFA). mp. 156 °C.

Example 305: N-[3-(3,5-Dimethyl-4-isoxazolyl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was prepared in a similar manner as described in Example 303 starting from N-(3-bromo-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester. MS m/z: 569 (MH^+) mp. 144.8 °C

Example 306: N-[4-(1,3-thiazol-2-yl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

1) To a solution of N-(4-bromo-2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (0.240 g) in toluene (10 mL) was added 2-tributylstannio-1,3-thiazole (0.52 g) and $Pd(PPh_3)_4$ (0.11 g) and the solution was heated to 80 °C under N_2 for 24 h. It was worked up and purified in a similar manner as described in Example 135-3) to yield 30 mg of N-[4-(1,3-thiazol-2-yl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester . ESMS: m/z 571 (MH^+).

2) The product obtained above was hydrolyzed in a similar method as described in Example 1-5) to yield the title compound (22.7 mg). ESMS: m/z 557 (MH^+). mp. 141.9 °C.

Example 307: N-[4-(1,3-Thiazol-4-yl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

The title compound was prepared in a manner analogous to Example 306 by replacing 2-tributylstannio-1,3-thiazole with 4-tributylstannio-1,3-thiazole. ESMS: m/z 557 (MH^+) and 555 (M^- -H). mp. 186.5 °C.

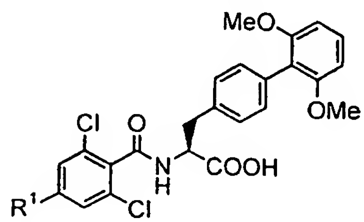
Example 308: N-[4-(2-Pyrazinyl)-2,6-dichlorobenzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine.

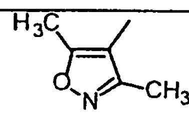
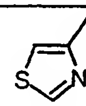
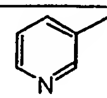
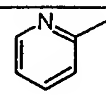
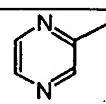
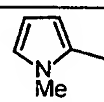
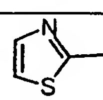
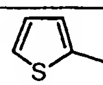
The title compound was prepared in a manner analogous to Example 306 by replacing 2-tributylstannio-1,3-thiazole

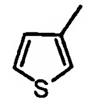
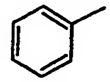
with 2-tributylstanniopyrazine. ESMS: m/z 552 (MH^+). mp. 145.7 °C.

The following compounds (Examples 309-318) were prepared in a similar method as described in Example 303.

TABLE 23



Example	R^1	m/z (MH^+)
309		569
310		558
311		551
312		551
313		552
314		553
315		557
316		556

317		557
318		550

Example 319: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-3-(morpholinomethyl)phenyl]-L-phenylalanine

1) 2,6-Dimethoxy-3-(hydroxymethyl)benzeneboronic acid was coupled with N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester in a similar method as described in Example 7-2) to give N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-3-(hydroxymethyl)phenyl]-L-phenylalanine ethyl ester.

2) Thionyl chloride (100 mL) was added to an ice-cold solution of the product obtained above (0.212 mg) in CH_2Cl_2 (5 mL) under N_2. The mixture was stirred for 1 hour at room temperature and evaporated. The residue was dissolved in CH_2Cl_2, evaporated, and dried under vacuum to give N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-3-(chloromethyl)phenyl]-L-phenylalanine ethyl ester as a crude product (0.22 g).

3) A solution of the product obtained above (0.22g) in DMF (5 mL) was added to an ice-cold solution of morpholine (41 mg) in DMF (1 mL) containing Et_3N (0.111 mL) under N_2. The mixture was stirred for 14 hours at room temperature and then partitioned between EtOAc and water. The EtOAc layer was separated and washed successively with satd. $NaHCO_3$, water and brine, dried and evaporated. The residue was purified by column chromatography (silica gel; eluent: EtOAc) to give 0.186 g of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-3-(morpholinomethyl)phenyl]-L-phenylalanine ethyl ester. ESMS: m/z 601 (MH^+).

4) The product obtained above was hydrolyzed in a similar method as described in Example 1-5) to give the title compound. ESMS: m/z 573 (MH^+). mp. 241-242 °C.

Example 320: N-(2,6-Dichloro-4-fluorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was prepared in a similar method as described in Example 2. MS m/z 492 (MH^+), mp.206-207 °C.

Example 321: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-4-(trifluoromethyl)phenyl]-L-phenylalanine

The title compound was prepared in a similar method as described in Example 2.

MS m/z 542 (MH^+), mp. 231-232 °C.

Example 322: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxy-3-bromophenyl)-L-phenylalanine

1) N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (1.01 g) was dissolved in CH_2Cl_2 (40 mL) under N_2 and tetrabutylammonium tribromide (1.21 g) was added and the mixture was stirred at room temperature overnight. More tetrabutylammonium tribromide (0.55 g) was added and the mixture was stirred for 1 day. The mixture was then washed with water (25 mL) and the organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: hexane and AcOEt) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-bromophenyl)-L-phenylalanine methyl ester (1.17 g).

2) The product obtained above was hydrolyzed in a similar manner as describe in Example 1-5) to give the title compound. MS m/z 555 (MH^+), mp. 205-206 °C

Example 323: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxy-3-aminophenyl)-L-phenylalanine

1) N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (1.59 g) was dissolved in THF (4 mL) under N_2 then 70% HNO_3 (4 mL) was added and the mixture was stirred at 50 °C overnight. The mixture was diluted with AcOEt (150 mL) and washed with water (100 mL). The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was dissolved in anhydrous MeOH (100 mL) and dry HCl gas was bubbled through the mixture at 0 °C for a few minutes. The mixture was stirred at room temperature overnight, concentrated, taken up with AcOEt and washed with 1N HCl, satd. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated. The crude product was purified by flash column chromatography (silica gel; eluent: hexanes and AcOEt) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-nitrophenyl)-L-phenylalanine methyl ester (1.1 g).

2) The product obtained above was dissolved in EtOH (40 mL), and $Na_2S_2O_4$ (2.6 g) in water (5 mL) was added. The mixture was refluxed for 2 hours and concentrated. The residue was taken up with AcOEt and washed with brine. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by preparative TLC (silica gel; eluent: hexanes and AcOEt) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-aminophenyl)-L-phenylalanine methyl ester (0.31 g).

3) The product obtained above was hydrolyzed in a similar method as described in Example 1-5) to give the title compound. MS m/z 542 (MH^+), mp. 231-232 °C.

Example 324: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-3-(methylureido)phenyl]-L-phenylalanine

The title compound was obtained in a similar procedure as described in Example 70 by reacting N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-aminophenyl)-L-phenylalanine methyl ester with MeNCO instead of MeNCS. MS m/z 546 (MH^+), mp. 236-237 °C.

Example 325: N-(2,6-Dichlorobenzoyl)-4-[2,6-dimethoxy-3-(acetylamino)phenyl]-L-phenylalanine

The title compound was obtained in a similar procedure as describe in Example 67 by reacting N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-aminophenyl)-L-phenylalanine methyl ester with acetyl chloride. MS m/z 531 (MH^+), mp. 244-245 °C.

Example 326: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxy-3-carbamoylphenyl)-L-phenylalanine

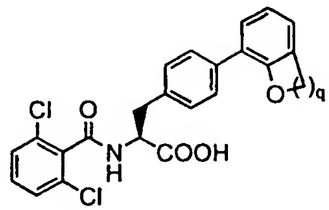
1) N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine methyl ester (150 mg) was dissolved in MeCN (6 mL) under N_2 and chlorosulfonyl isocyanate (45 μL) was added, and the mixture was stirred at room temperature for 2.5 h. The mixture was concentrated and 1N HCl (8 mL) was added. The mixture was stirred at room temperature overnight, extracted with AcOEt, dried ($MgSO_4$), filtered and evaporated. The crude product was purified by preparative TLC (silica gel; eluent: AcOEt) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-3-carbamoylphenyl)-L-phenylalanine methyl ester (156 mg).

2) The product obtained above was hydrolyzed in a similar method as described in Example 1-5) to give the title compound. MS m/z 517 (MH^+), mp. 227-228 °C.

The following compounds (Examples 327-328)were made from 7-bromo-2,3-dihydrobenzo[*b*]furan and 8-bromo-3,4-dihydro-*2H*-benzopyran respectively (Kerrigan, F., Martin,

C., Thomas, G. H., *Tet. Lett.* **1998**, *39*, 2219-2222), in a similar procedure as described in Example 7.

TABLE 24



Example	q	ms MH^+	mp °C
327	2	456	215-216
328	3	470	214-215

Example 329: N-(2,6-Dichlorobenzoyl)-4-(1-tert-butoxycarbonyl-2-pyrrolyl)-L-phenylalanine

The title compound was prepared in a similar method as described in Example 7 using 1-(*t*-butoxycarbonyl)pyrrole-2-boronic acid (Frontier Scientific). MS m/z 503 (MH^+), mp. 98-99 °C

Example 330: N-(2,6-Dichlorobenzoyl)-4-(3,5-dimethyl-4-isoxazolyl)-L-phenylalanine

The title compound and methyl ester were prepared in a similar method as described in Example 7. MS m/z 433 (MH^+), mp. 119 °C.

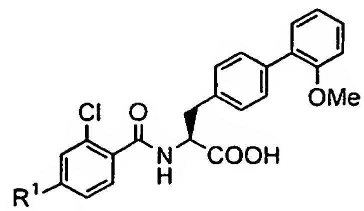
Methyl ester of the title compound: MS m/z 447 (MH^+), mp. 152 °C.

Example 331: N-(2,6-Dichloro-3-bromobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine

The title compound was prepared in a similar method as described in Example 322. MS m/z 553 (MH^+), mp. 234.8 °C.

The following compounds (Examples 332-335) were prepared in a similar method as described in Example 2.

TABLE 25



Example	R^1	MS, m/z	mp., °C
332	CH_3NH-	439 (MH^+)	82.8
333	$CH_3SO_2N(CH_3)-$	517 (MH^+)	79.3
334	$(CH_3)_2SO_2NH-$	532 (MH^+)	128.1

Example 335: N-[2-Chloro-4-(methansulfonylamino)benzoyl]-4-[2-(trifluoromethyl)phenyl]-L-phenylalanine

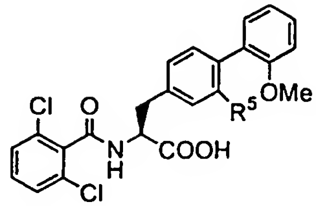
The title compound was prepared in a similar manner as described in Example 3. MS: m/z 541 (MH^+), mp. 114°C.

Example. 336: N-(2,6-Dichlorobenzoyl)-3-chloro-4-(2-methoxyphenyl)-L-phenylalanine

The title compound was prepared in a similar method as described in Example 1 using N-(tert-butoxycarbonyl)-3-chloro-L-tyrosine methyl ester. ESMS m/z 479 (MH^+), mp. 131°C.

The following compounds (Examples 337-339) were prepared in a similar method as described in Example 71.

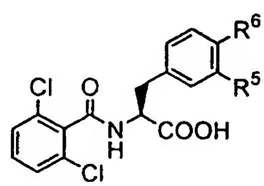
TABLE 26

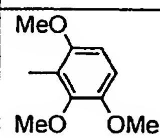
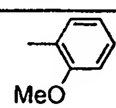
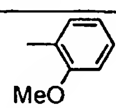


Example	R^5	MS m/z (MH^+)	mp., °C
337	$-COCH_2CH_3$	500	118-119
338	$-CO(CH_2)_3CH_3$	528	117.6
339	$-CO(CH_2)_5CH_3$	556	86-88

The following compounds (Examples 340-342) were prepared in a similar method as described in Example 73.

TABLE 27



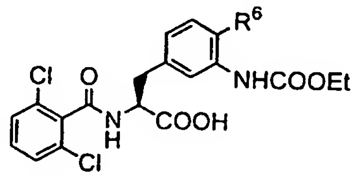
Example	R^5	R^6	MS m/z (MH^+)	mp., °C
340	$-CH(OH)CH_3$		548	121-123
341	$-CH(OH)CH_2CH_3$		502	117-119
342	$-CH(OH)(CH_2)_3CH_3$		528 $(M-H)^-$	158-159

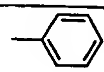
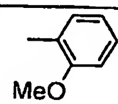
Example 343: N-(2,6-Dichlorobenzoyl)-3-acetylamino-4-phenyl-L-phenylalanine

The title compound was prepared in a similar procedure as described in Example 80. ESMS m/z 471 (MH^+).

The following compounds (Examples 344-345) were prepared in a similar procedure as described in Example 64 using ethyl chloroformate.

TABLE 28



Example	R°	MS m/z (MH^+)
344		501
345		531

Example 346: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxy-4-hydroxyphenyl)-L-phenylalanine

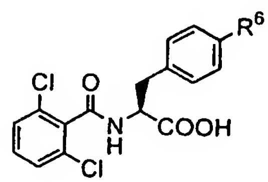
1) A mixture of 2,6-dimethoxy-4-(tert-butyl-diphenylsilyloxy)benzeneboronic acid (3 g), N-(2,6-dichlorobenzoyl)-4-bromo-L-phenylalanine ethyl ester (0.8 g), $Pd(PPh_3)_4$ (1 g) and K_2CO_3 (2.1 g) in DME/H_2O (20 mL/0.5 mL) was heated at 80 °C for 6 hour under N_2. The mixture was diluted with EtOAc and washed with water, dried and evaporated. The residue was dissolved in EtOAc and the solution was filtered through a silica gel column and evaporated. The residue was dissolved in THF, and TBAF (1.6 M in THF, 4ml) was added. The mixture was stirred at room temperature for 1 hour, diluted with water and extracted with EtOAc. The extract was washed with water, dried and evaporated. The residue was purified by flash column

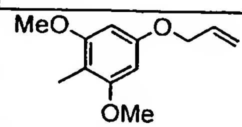
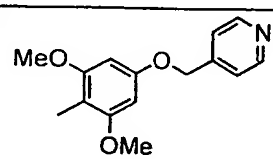
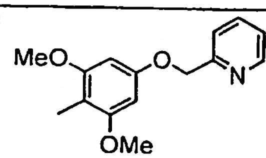
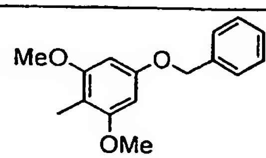
chromatography (silica gel; eluent: EtOAc/hexane 1/2) to yield 0.5g of N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxy-4-hydroxyphenyl)-L-phenylalanine ethyl ester. ESMS m/z: 490 (MH^+).

2) The product obtained above (0.05 g) was hydrolyzed with LiOH in a similar method as described in Example 1-5) to give 0.04 g of the title compound. ESMS m/z: 490 (MH^+).

The following compounds (Examples 347-350) were prepared in a similar procedure as described in Example 32.

TABLE 29



Example	R^6	MS m/z (MH^+)
347		530
348		581
349		581
350		580

Example 351: N-(2,6-Dichlorobenzoyl)-3-[1-(hydroxyimino)ethyl]-4-(2-methoxyphenyl)-L-phenylalanine

1) To a solution of N-(2,6-dichlorobenzoyl)-3-acetyl-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (0.15 g) in n-BuOH (5 mL) were added NH_2OH HCl salt (23 mg) and NaOAc (40 mg). The mixture was refluxed for 6 hour, then evaporated. The residue was diluted with CH_2Cl_2, washed with 1N HCl, dried and evaporated. The residue was purified by preparative TLC (silica gel; eluent: EtOAc/hexane 1:1) to give N-(2,6-dichlorobenzoyl)-3-[1-(hydroxyimino)ethyl]-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester. ESMS: m/z 490 (MH^+).

2) The product obtained above was hydrolyzed with LiOH in a similar manner as described in Example 1-5) to give the title compound. ESMS: m/z 501 (MH^+).

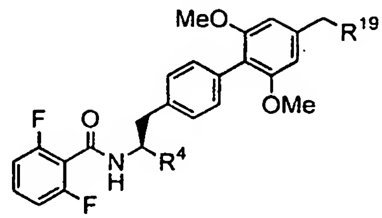
Example 352: N-(2,6-Dichlorobenzoyl)-3-[1-(methoxyimino)ethyl]-4-(2-methoxyphenyl)-L-phenylalanine

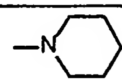
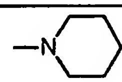
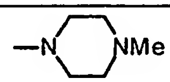
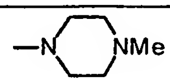
1) To a solution of N-(2,6-dichlorobenzoyl)-3-acetyl-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester (0.12 g) in EtOH (5 mL) were added NH_2OMe HCl salt (24 mg) and DIEA (60 mg). The mixture was refluxed for 2h and evaporated. The residue was diluted with EtOAc, washed with 1N HCl, dried, and evaporated. The residue was purified by preparative TLC (silica gel; eluent: EtOAc/hexane 2:1)to give 0.058 g of N-(2,6-dichlorobenzoyl)-3-[1-(methoxyimino)ethyl]-4-(2-methoxyphenyl)-L-phenylalanine ethyl ester. ESMS: m/z 534 $(M-H)^-$.

2) The product obtained above was hydrolyzed with LiOH in a similar manner as described in Example 1-5) to give 0.04 g of the title compound. ESMS: m/z 513 $(M-H)^-$, mp. 106.8 °C.

The following compounds (Examples 353-356) were prepared in a similar method as described in one of above Examples:

TABLE 30



Example	R^4	R^{19}	ESMS m/z (MH^+)	mp. °C
353	COOH		538	232
354	COOEt	 .HCl	567	150
355	COOH		553	225
356	COOEt	 2 HCl	582	226

Example 357: N-(2,6-Dichlorobenzoyl-4-[2,6-dimethoxy-4-(succinimidomethyl)phenyl]-L-phenylalanine

1) DEAD (0.13 mL) was added to an ice-cooled solution of N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(hydroxymethyl)phenyl]-L-phenylalanine tert-butyl ester (250 mg), triphenylphosphine (175 mg) and succinimide (90 mg) in THF (3mL) under N_2. The mixture was stirred at 0°C for 30 min, and warmed to room temperature and stirred for 2h. The mixture was partitioned between H_2O and EtOAc, and the aqueous layer was extracted with EtOAC. The combined

organic layer was dried ($MgSO_4$), and concentrated *in vacuo*. The residue was purified by preparative TLC (silica gel; eluent: EtOAc/hexane 1:1) to give N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(succinimidomethyl)phenyl]-L-phenylalanine tert-butyl ester (138 mg).

2) TFA (2 mL) was added to a solution of the product obtained above (120 mg) in CH_2Cl_2 (4 mL). The mixture was stirred at room temperature for 3 days, and the mixture was concentrated *in vacuo*. The residue was purified by column chromatography (silica gel; eluent: CH_2Cl_2/MeOH 95:5) and recrystallization from EtOH/H_2O to give the title compound (61 mg). mp. 137°C. ESMS: m/z 608 $[M+Na]^+$.

Example 358: N-(2,6-Dichlorobenzoyl)-4-(2,6-dimethoxy-4-[(3-methyl-2,5-dioxo-1-imidazolidinyl)methyl]phenyl]-L-phenylalanine

The title compound was prepared in a similar procedure as described in Example 357, but replacing succinimide with 1-methylhydantoin. mp. 248°C, ESMS: m/z 624 $[M+Na]^+$.

Example 359: N-(2,6-Dichlorobenzoyl)-4-(6-methoxy-2-hydroxyphenyl)-L-phenylalanine

N-(2,6-Dichlorobenzoyl)-4-(6-methoxy-2-hydroxyphenyl)-L-phenylalanine ethyl ester was hydrolyzed with LiOH in a similar method as described in Example 1-5) to give the title compound. mp. 224.4°C, ESMS: m/z 460 (MH^+), 458 $(M-H)^-$.

Example 360: N-(2,6-Dichlorobenzoyl)-4-(2,6-dihyroxyphenyl)-L-phenylalanine

1) 2,6-Di(methoxymethoxy)benzeneboronic acid (0.25 g) was coupled with N-(2,6-dichlorobenzoyl)-O-(trifluoromethanesulfonyl)-L-tyrosine ethyl ester in a similar procedure as described in Example 5-3) to afford N-

(2,6-dichlorobenzoyl)-4-[2,6-di(methoxymethoxy)phenyl]-L-phenylalanine ethyl ester. ESMS: m/z 562 (MH^+).

2) To a solution of the product obtained above (0.076 g) in EtOH (5 mL) was added HCl (4N in dioxane, 1.2 mL) and the mixture was stirred under N_2 for 4 hours at room temperature. The mixture was evaporated to give N-(2,6-dichlorobenzoyl)-4-(2,6-dihyroxyphenyl)-L-phenylalanine ethyl ester (61.6 mg). ESMS: m/z 474 (MH^+).

3) The product obtained above (61.6 mg) was hydrolyzed with LiOH (33.8 mg) in a similar manner as described in Example 1-5) to give N-(2,6-dichlorobenzoyl)-4-(2,6-dihydroxyphenyl)-L-phenylalanine (58.3 mg). ESMS: m/z 446 (MH^+), 444 $(M-H)^-$, mp. 238°C.

Reference Examples

Reference Example 1: 2,6-Dichlorobenzeneboronic acid

1-Bromo-2,6-dichlorobenzene (2.00g) was dissolved in freshly distilled THF (7 mL). This solution was cooled to -78°C and n-BuLi (8.3 mL of a 1.6M solution in hexane) was added dropwise to the cold solution under N_2. The mixture was stirred for 5 min at -78°C and $(MeO)_3B$ (2.2 mL) was added. The resulting mixture was allowed to warm to room temperature and stirred overnight. Water was added and the resulting mixture was stirred for 0.5 h, then acidified with HOAc and extracted with EtOAc. The organic layer was further washed with water and brine, dried ($MgSO_4$) filtered and evaporated to yield 2,6-dichlorobenzeneboronic acid (1.6 g).

Reference Example 2: 2,6-Dicyanobenzeneboronic acid:

1,3-Dicyanobenzene (1.00 g) was dissolved in freshly distilled THF (70 mL). This solution was cooled to -96 °C and LDA (4.2 mL of a 2M solution) was added dropwise to the

cold solution under N_2. The mixture was stirred for 30 min at -96 °C and $(MeO)_3B$ (1.3 mL) was added. The resulting mixture was allowed to warm to room temperature and stirred overnight. Water was added and the resulting mixture was stirred for 0.5 h, then acidified with HOAc and extracted with EtOAc. The organic layer was further washed with water and brine, dried ($MgSO_4$), filtered and evaporated. The residue was taken up in CH_2Cl_2, filtered and evaporated to yield 2,6-dicyanobenzeneboronic acid(0.56 g).

Reference Example 3: 2,6-Dimethoxy-4-propylbenzeneboronic acid.

1) Ethyltriphenylphosphonium bromide (4.69 g) was dissolved in anhydrous THF (70 mL) and the mixture cooled to 0-5 °C. *n*-BuLi (5.05 mL of 2.5 M in hexane) was added dropwise and the resulting mixture was stirred at room temperature for 3 h. The mixture was cooled to -78 °C and a solution of 3,5-dimethoxybenzaldehyde (2 g) in anhydrous THF (14 mL) was added. The mixture was allowed to warm up to room temperature then stirred overnight. The mixture was concentrated, and the residue was taken up with AcOEt, washed with water and brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane and AcOEt 10:1) to give 3,5-dimethoxy-1-(1-propenyl)benzene as a mixture of *cis* and *trans* isomers (2.15 g).

2) The product obtained above was dissolved in EtOH (60 mL) and 10% Pd/C (215 mg) was added. The mixture was stirred under H_2 atmosphere for 19 h. The mixture was passed through a silica pad using CH_2Cl_2 as solvent, and evaporated to give 3,5-dimethoxy-1-propylbenzene (1.76 g).

3) The product obtained above was converted to the title compound by following the procedure similar to Example

7-(1) but replacing 1,3-dimethoxy benzene with 3,5-dimethoxy-1-propylbenzene.

Reference Example 4: 2,6-Dimethoxy-4-trifluoromethylbenzeneboronic acid

1) 3-Methoxy-5-(trifluoromethyl)aniline (5 g) was suspended in 20% HCl (200 mL), stirred for 30 min, cooled to 0-5 °C and diazotized with $NaNO_2$ (2.17 g) added in small portions. The mixture was stirred for 30 min at that temperature and added dropwise to boiling water (200 mL). The mixture was refluxed for 15 min, allowed to cool to room temperature and extracted with AcOEt, dried ($MgSO_4$), filtered and evaporated. The residue was then purified by column chromatography (silica gel; eluent: hexane and AcOEt) to give 3-methoxy-5-(trifluoromethyl)phenol (3.6 g)

2) The product obtained above was dissolved in acetone (20 mL). K_2CO_3 (5.18 g) and MeI (1.75 mL) were added. The mixture was stirred under N_2 at room temperature for 2 days, evaporated, taken up with water (50 mL), extracted with CH_2Cl_2, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane/AcOEt 10:1 to 1:1) to give the desired 3,5-dimethoxy-α,α,α-trifluorotoluene (2.97 g).

3) The product obtained above was converted to the title compound by following the procedure similar to Example 7-(1) but replacing 1,3-dimethoxybenzene by 3,5-dimethoxy-α,α,α-trifluorotoluene.

Reference Example 5: 4-(1,3-Dioxolan-2-yl)-2,6-dimethoxybenzeneboronic acid

1) 4-bromo-3,5-dimethoxybenzaldehyde (3 g) was dissolved in toluene (50 mL) and ethylene glycol (6.8 mL) and a catalytic amount of *p*-TSA were added. The mixture was refluxed overnight using a Dean Stark apparatus and

evaporated. The residue was purified by column chromatography (silica gel; eluent hexane/AcOEt 5:1 to 2:1) to give 4-bromo-3,5-dimethoxybenzaldehyde ethylene acetal (2.63 g).

2) The product obtained above was treated in a similar procedure as described in Example 7-1) to give the title compound.

Reference Example 6: 2,6-Dimethoxy-3-methoxymethoxybenzeneboronic acid

1) To anhydrous K_2CO_3 (3.55 g) in acetone (10 mL) under N_2 was added 2,4-dimethoxyphenol (3.3 g, *J.O.C.* **1984**, *49*, 4740) in acetone (20 mL). Chloromethyl methyl ether (1.79 mL) was added dropwise and the mixture was stirred at room temperature for 18 h then heated to 50 °C for 24 h. Additional quantity of chloromethyl methyl ether (1.79 mL) was added and the mixture was stirred for another day at 50 °C and evaporated. The residue was taken up with water and extracted with AcOEt. The extract was dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane/AcOEt 20:1 to 10:1) to give 1,3-dimethoxy-4-methoxymethoxybenzene (1.18 g).

2) The product obtained above was treated in a similar procedure as described in Example 7-1) replacing 1,3-dimethoxy benzene by 1,3-dimethoxy-4-methoxymethyloxybenzene to give the title compound.

Reference Example 7: 6-Methoxy-1,4-benzodioxan-5-ylboronic acid

1) 1,4-Benzodioxan-6-carboxaldehyde (5.20 g) was dissolved in MeOH (60 mL) containing conc. H_2SO_4 (0.6 mL). At 0 °C an aqueous solution of 30% H_2O_2 (4.7 mL) was added to the mixture over 5 minutes. The mixture was warmed to room

temperature, stirred an additional 18 h and evaporated. The residue was taken up with H_2O and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane to hexane/ EtOAc 3:1) to give 6-hydroxy-1,4-benzodioxan (3.85 g). ESMS: m/z 153 MH^+.

2) To the mixture of the product obtained above (3.83 g), K_2CO_3 (7.0 g) and *n*-Bu_4NI (186 mg) in DMF (10 mL) was added iodomethane (2.3 mL) and the mixture was stirred at room temperature under N_2 for 24 h, filtered and washed with EtOAc (3 x 15 mL). The filtrate was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (silica gel; eluent hexane to hexane/EtOAc 4:1) to give 6-methoxy-1,4-benzodioxan (3.25 g). ESMS: m/z 167 (MH^+).

3) The product obtained above was converted to the title compound by a similar method as described in Example 7-(1).

Reference Example 8: 6-Methoxy-2-methoxymethoxybenzeneboronic acid

The title compound was prepared from 3-methoxyphenol by a similar method as described in Reference Example 6.

Reference Example 9: 2,6-Dimethoxy-4-[(t-butyldiphenylsilyloxy)methyl]benzeneboronic acid

1) A mixture of 3,5-dimethoxybenzyl alcohol (4.0 g), t-butyl-diphenylsilyl chloride (6.54 g) and imidazole (3.28 g) in DMF (60 mL) was stirred at room temperature for 24 h. DMF was evaporated and the residue was purified by column chromatography (silica gel; eluent: hexane to hexane/EtOAc 20%) to yield 8.5 g of 3,5-dimethoxy-1-[(t-butyldiphenylsilyloxy)methyl]benzene. ESMS: m/z 407 (MH^+).

2) The product obtained above was treated in a similar procedure as described in Example 7-1) to give the title compound. ESMS: m/z 451 (MH^+).

Reference Example 10: 2,6-Dimethoxy-4-(thiomorpholinomethyl)benzeneboronic acid

1) Thiomorpholine (3.4 g) was added to a solution of 3,5-dimethoxybenzyl chloride (2 g) in THF (25 mL) and the mixture was stirred overnight at room temperature. The solid material was removed by filtration and the filtrate was evaporated. The residue was purified by column chromatography (silica gel; eluent: EtOAc/hexane 1/2) to yield 2 g of 3,5-dimethoxy-1-(thiomorpholino-methyl)benzene. ESMS: m/z 253 (M).

2) The product obtained above was treated in a similar procedure as described in Example 7-1) to give the title compound.

Reference Example 11: 2,6-Dimethoxy-4-[(4-tert-butoxycarbonylpiperazinyl)methyl]benzeneboronic acid

The title compound was prepared in a similar procedure as described in Reference Example 10 but replacing thiomorpholine with N-(tert-butoxycarbonyl)piperazine.

The following compounds (Reference Example 12-17) were prepared in a similar method as described in Reference Example 10 by replacing thiomorpholine with the requisite amines.

Reference Example 12: 2,6-Dimethoxy-4-[(diethylamino)methyl]benzeneboronic acid

Reference Example 13: 2,6-Dimethoxy-4-(piperidinomethyl)benzeneboronic acid

Reference Example 14: 2,6-Dimethoxy-4-(morpholinomethyl)benzeneboronic acid

Reference Example 15: 2,6-Dimethoxy-4-[(4-benzyl-1-piperazinyl)methyl]benzeneboronic acid

Reference Example 16: 2,6-Dimethoxy-4-[(dimethylamino)methyl]benzeneboronic acid

Reference Example 17: 2,6-Dimethoxy-4-[(4-tert-butoxycarbonylpiperazinyl)methyl]benzeneboronic acid

Reference Example 18: 2,6-Dimethoxy-4-(2-hydroxyethyl)benzene boronic acid

1) A solution of (3,5-dimethoxy)phenylacetic acid (3 g) in Et_2O (100 mL) was cooled to 0 °C and $LiAlH_4$ (1M in Et_2O, 16.8 mL) was added. The mixture was warmed to room temperature and stirred for 5 h, whereupon the pH was adjusted to 5 using HCl (1 M). The mixture was washed with H_2O/EtOAc and the organic layer was separated. The aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to give 3,5-dimethoxy-4-(2-hydroxyethyl)benzene (2.8 g) as a crude product.

2) The product was treated in a similar procedure as described in Example 7-1) to give the title compound.

Reference Example 19: 2,6-Dimethoxy-4-(tert-butyl-diphenylsilyloxy)benzeneboronic acid

1) A mixture of 3,5-dimethoxybenzyl alcohol (4.0 g), tert-butyl-diphenylsilyl chloride (6.54 g) and imidazole (3.28 g) in DMF (60 mL) was stirred at room temperature for 24 h. DMF was evaporated and the residue was purified by column chromatography (silica gel; eluent: hexane to

hexane/ EtOAc 20%) to yield 8.5 g of 3,5-dimethoxybenzyl tert-butyldiphenylsilyl ether. ESMS: m/z 407 (MH^+).

2) The product obtained above was treated in a similar procedure as described in Example 7 to give the title compound. ESMS: m/z 451 (MH^+).

Reference Example 20: 2,6-Dimethoxy-4-hydroxymethylbenzeneboronic acid.

3,5-Dimethoxybenzyl alcohol was treated in a similar procedure as described in Example 7 to yield the title compound.

Reference Example 21: 2,6-Dimethoxy-3-hydroxymethylbenzeneboronic acid

The title compound was prepared in a similar method as described in Example 7 from 2,4-dimethoxybenzylalcohol.

Reference Example 22: 1-Bromo-2,4-dimethoxy-6-cyanobenzene

To a solution of 3,5-dimethoxybenzonitrile (2 g) in CH_2Cl_2 (100 mL) was added pyridinium tribromide (4 g). The mixture was stirred for 24h at room temperature then washed successively with aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) filtered and evaporated. The residue was crystallized from CH_2Cl_2 and hexane to yield the title compound (1.8 g).

Reference Example 23: N-Allyl-N-tert-butoxycarbonyl-4-bromo-3,5-dimethoxyaniline

1) 3,5-Dimethoxyaniline (7.55 g) was dissolved in CH_2Cl_2 (100 mL) under N_2 and the solution was cooled to -78 °C. A solution of tetrabutylammonium tribromide (25 g) in CH_2Cl_2 (100 mL) was added and the mixture was stirred at that temperature for 45 min. The mixture was allowed to warm up to room temperature, stirred for 1.5 h and extracted

with 1N HCl. The extract was neutralized with 3 N NaOH and extracted with AcOEt. The extract was dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane /AcOEt 4:1 to 2:3) to give 4-bromo-3,5-dimethoxyaniline (3.76 g).

2) The product obtained above (3g) was then dissolved in anhydrous THF (25 mL) under N_2 and DIEA (5.4 mL) was added. A solution of di-tert-butyl dicarbonate (3.39 g) in anhydrous THF (20 mL) was added and the mixture was stirred at 45 °C for 3.5 days. The solvent was evaporated and the residue was taken up with AcOEt, washed successively with 1N HCl, sat. $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent hexane /AcOEt 4:1) to give a solid. The solid was triturated with hexane to remove remaining di-tert-butyl dicarbonate and N-tert-butoxycarbonyl-4-bromo-3,5-dimethoxyaniline was isolated by filtration (3.67 g).

3) NaH (60%, 0.585 g) was added to a solution of the product obtained above in anhydrous THF/DMF (100 /6 mL) and the mixture was stirred for a few minutes. Allyl bromide (1.13 mL) was added and the mixture was stirred at room temperature overnight, concentrated and the residue was purified by column chromatography (silica gel; eluent: hexane/AcOEt 4:1) to give the title compound (3.96 g).

Synthesis of Benzoic acids:

Reference Example 24: 4-Amino-2,6-dichlorobenzoic acid methyl ester.

1) To 2,6-dichloro-4-nitrobenzoic acid (12.8 g, US patent 3,423,475) was added anhydrous CH_2Cl_2 (60 mL) and thionyl chloride (40 mL) then the resulting mixture was refluxed for 19 h. The mixture was allowed to cool to room temperature and evaporated. Additional CH_2Cl_2 (10 mL) was

added and the solution was evaporated. MeOH (100 mL) was added to the residue and the mixture was refluxed for 17 h. The mixture was allowed to cool to room temperature and placed in an ice-bath. The precipitated solid was collected by filtration to give methyl 2,6-dichloro-4-nitrobenzoate (10.8 g, 80%).

2) To a mixture of the product obtained above in EtOH (250 mL) was added a solution of $Na_2S_2O_4$ (45 g) in water (100 mL). The mixture was refluxed for 2 h, stirred at room temperature overnight, filtered and concentrated. The residue was dissolved in 1N HCl (250 mL), stirred for 2 h, neutralized with 10% NaOH and extracted with AcOEt. The extract was dried ($MgSO_4$), filtered and evaporated. The residue was recrystallized from AcOEt/hexane to give the title compound (7.48 g).

Reference Example 25: 4-Bromo-2,6-dichlorobenzoic acid and 4-bromo-2,6-dichloro benzoyl chloride.

1) 4-Amino-2,6-dichlorobenzoic acid methyl ester (1.00 g) was suspended in 40% aq. HBr and the mixture was cooled lto 0-5 °C. After $NaNO_2$ (376 mg) was added in small portions, the mixture was stirred for about 5 min. Copper (100 mg) was added and the mixture was warmed up to 100 °C. The mixture was then stirred at 100 °C for 30 min, diluted with water and extracted with AcOEt. The extract was dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane and AcOEt 50:1) to give 4-bromo-2,6-dichlorobenzoic acid methyl ester (1.07 g).

2) The product obtained above (1.06 g) was dissolved in THF/MeOH (50 mL, 6:1) and LiOH (1M, 7.47 mL) was added. The mixture was refluxed for 1 day, evaporated, and the residue was taken up with water (50 mL) and acidified to pH < 2 with 1N HCl. The mixture was extracted with AcOEt, dried

($MgSO_4$), filtered and evaporated to give 4-bromo-2,6-dichlorobenzoic acid (0.94 g).

3) To a solution of the product obtained above in CH_2Cl_2 (20 mL), was added thionyl chloride (2.51 mL). The mixture refluxed for 5 h, evaporated, and coevaporated with CH_2Cl_2 to give 4-bromo-2,6-dichlorobenzoyl chloride.

Reference Example 26: 2,6-Dichloro-4-hydroxybenzoic acid

1) 4-Amino-2,6-dichlorobenzoic acid methyl ester (0.5 g) was suspended in 20% HCl (25 mL) and stirred for 30 min then cooled to 0-5 °C. After slow addition of $NaNO_2$ (188 mg), the mixture was stirred for 30 min at that temperature and added to boiling water (50 mL). The mixture was then refluxed for 2 h, allowed to cool to room temperature and extracted with AcOEt, dried ($MgSO_4$), filtered and evaporated. The residue was purified by preparative TLC (silica gel; eluent: CH_2Cl_2) to give 2,6-dichloro-4-hydroxybenzoic acid methyl ester (275 mg).

2) To a solution of the product obtained above (265 mg) in THF/MeOH (25 mL, 6:1) was added 1N NaOH (3.6 mL), and the mixture was refluxed for 1day. 1N NaOH (3.6 mL) was added and the mixture was refluxed for another day. The mixture was evaporated and the residue was taken up with water, acidified to pH < 2 with 1 N HCl and extracted with AcOEt containing a little amount of MeOH . The extract was dried ($MgSO_4$), filtered and evaporated to give the title compound (248 mg).

Reference Example 27: 2,6-Dichloro-4-fluorobenzoic acid.

4-Amino-2,6-dichlorobenzoic acid methyl ester (0.5 g) was suspended in 15% HCl (10 mL) and stirred for 30 min then cooled to 0-5 °C. After addition of $NaNO_2$ (188 mg) in small portions, the mixture was stirred for 30 min at that temperature. Precooled HBF_4 (0.46 mL) was added and the

mixture was stirred for 30 min. The resulting precipitate was collected and washed successively with cold water, MeOH and ether. The solid was then dried over conc. H_2SO_4 in a vacuum dessicator for a few days. The solid was heated with a bunsen burner until all the solid has melted. The resulting fumes were collected over water (distilling apparatus). The product was then recovered with Et_2O. The solvent was evaporated and the crude product was purified by preparative TLC (silica gel; eluent: hexane/AcOEt 50:1 to 20:1) to give 2,6-dichloro-4-fluorobenzoic acid methyl ester (241 mg).

2) To a solution of the product obtained above (233 mg) in CCl_4 was added TMSI (164 mL). The mixture was then stirred under N_2 at 50 °C for 2 days. Water was added and the mixture was stirred for 1h. 1N HCl (25 mL) was added and the mixture was extracted with AcOEt. The extract was dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: $CHCl_3$/MeOH gradient) to give the title compound (38 mg).

Reference Example 28: 2-Chloro-4-(2-thiazolinylamino)benzoic acid

1) A mixture of 4-amino-2-chlorobenzoic acid methyl ester (0.5 g) and 2-chloroethylisothiocyanate (0.26 mL) in THF (20 mL) was refluxed for 24 h. THF was distilled and the residue was purified by column chromatography (silica gel: eluent: hexane/EtOAc 3:1-1:1) to yield 2-chloro-4-(2-thiazolinylamino)benzoic acid methyl ester (74 mg). ESMS: m/z 271 (MH^+).

2) The product obtained above was hydrolyzed with LiOH to give the title compound (43 mg). ESMS: m/z 257 (MH^+).

Reference Example 29: 2-Chloro-4-(2-oxazolinylamino)benzoic acid

1) A mixture of 4-amino-2-chlorobenzoic acid methyl ester (0.5 g) and 2-chloroethylisocyanate (0.23 mL) in THF (20 mL) was heated under reflux for 24 h. THF was distilled and the residue was purified by column chromatography (silica gel; eluent: hexane/EtOAc 3:1-1:1) to yield 4-[3-(2-chloethyl)ureido]-2-chlorobenzoic acid methyl ester (0.63 mg). ESMS: m/z 291 (MH^+).

2) NaOMe (0.21g) was added to a solution of the product obtained above (0.58 g) in THF (20 mL) and the mixture was refluxed overnight. THF was distilled, and the residue was extracted with EtOAc. The extract was washed with water, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel; eluent: EtOAc) to yield 2-chloro-4-(2-oxazolidinylamino)benzoic acid methyl ester (0.46 g). ESMS: m/z 254 (MH^+).

3) The product obtained above was hydrolyzed with LiOH to give the title compound. ESMS: m/z 240 (MH^+).

Reference Example 30: 2-Chloro-4-(2-oxo-1-pyrrolidinyl)-benzoic acid.

1) To a solution of 4-amino-2-chlorobenzoic acid methyl ester hydrochloride (0.52 g) and DIEA (0.27 mL) in CH_2Cl_2 (20 mL) at 0 °C under N_2 was added 4-chlorobutyryl chloride (0.3 mL) and the mixture was stirred for 4 h at that temperature. DMAP (0.23 mmol) was added and the mixture was stirred at room temperature overnight. 4-Chlorobutyryl chloride (0.3 mL) and DIEA (0.09 mL) were added and the mixture was stirred for 24 h. The mixture was diluted with CH_2Cl_2 (100 mL) and the solution was washed successively with 1N HCl, std. $NaHCO_3$, brine, dried and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane/EtOAc 3:1) to yield 4-(4-chlorobutyryl)amino-2-chlorobenzoic acid methyl ester (0.64 g). ESMS: m/z 290(MH^+).

2) NaOMe (0.33 g) was added to a solution of the product obtained above (0.64 g) in THF (20 mL) and the mixture was refluxed for 3 h. THF was removed and the residue was partitioned between EtOAc and water. EtOAc layer was separated and the aqueous layer was extracted with EtOAc. The combined extract was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane/EtOAc 1:1) to yield 2-chloro-4-(2-oxo-1-pyrrolidinyl)benzoic acid methyl ester. ESMS: m/z 254 (MH^+).

3) The product obtained above was hydrolyzed with LiOH to give the title compound. ESMS: m/z 240 (MH^+).

Reference Example 31: 2-Chloro-4-(1-pyrrolyl)benzoic acid.

1) A mixture of 4-amino-2-chlorobenzoic acid methyl ester (0.46 g) and 2,5-dimethoxytetrahydrofuran (0.33 mL) in AcOH (16 mL) was heated under reflux for 2 h. The mixture was cooled to room temperature, diluted with water and extracted with EtOAc. The extract was washed with satd. $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane/EtOAc 5/1) to yield 0.48 g of 2-chloro-4-(1-pyrrolyl)benzoic acid methyl ester. ESMS: m/z 236 (MH^+).

2)The product obtained above was hydrolyzed with LiOH to give the title compound. ESMS: m/z 220 $(M-H)^-$.

Reference Example 32: 2-Chloro-4-(2-trifluoroacetyl-1-pyrrolyl)benzoic acid.

1) Trifluoroacetic anhydride (0.55 mL) was added to a solution of 2-chloro-4-(1-pyrrolyl)benzoic acid methyl ester (0.3 g) in CH_2Cl_2 (5 mL) and the mixture was stirred at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 and the mixture was stirred with satd. $NaHCO_3$ for 30 min. The organic layer was separated and washed with brine, dried

($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane/EtOAc 5/1) to yield 0.4 g of 2-chloro-4-(2-trifluoroacetyl-1-pyrrolyl)benzoic acid methyl ester. ESMS: m/z 330 (M-1).

2) The product obtained above was hydrolyzed with LiOH to give the title compound. ESMS: m/z 318 (MH^+).

Reference Example 33: 2-Chloro-4-(2,5-dichloro-1-pyrrolyl)-benzoic acid.

1) N-Chlorosuccinimide (0.56 g) was added under N_2 to an ice-cold solution of 2-chloro-4-(1-pyrrolyl)benzoic acid methyl ester (0.5 g) in THF (7 mL). The mixture was warmed up to room temperature and stirred overnight. THF was removed and the residue was treated with Et_2O and filtered. The filtrate was evaporated and the residue was purified by column chromatography (silica gel; eluent: hexane/EtOAc 10/1) to yield 0.61 g of 2-chloro-4-(2,5-dichloro-1-pyrrolyl)benzoic acid methyl ester. ESMS: m/z 306 (MH^+).

2) The product obtained above was hydrolyzed with LiOH to give the title compound. ESMS: m/z 290 (MH^+).

Reference Example 34: 2-Chloro-4-(2-formyl-1-pyrrolyl)benzoic acid.

1) A solution of DMF (0.1 mL) in CH_2Cl_2 (2 mL) was added dropwise with stirring to a solution of oxalyl chloride (0.2 mL) in CH_2Cl_2 (16 mL) at -30 °C under N_2. The mixture was stirred for 15 min and a solution of 2-chloro-4-(1-pyrrolyl)benzoic acid methyl ester (0.5 g) in DMF (4 mL) was added. The mixture was stirred at that temperature for 3 h and allowed to warm to room temperature. The mixture was stirred overnight and evaporated. The residue was partitioned between EtOAc and 0.2 M NaOAc. The EtOAc layer was separated and the aqueous solution was extracted with EtOAc. The combined EtOAc layer was washed with brine, dried ($MgSO_4$), filtered and evaporated. The residue was

purified by column chromatography (silica gel; eluent: hexane/EtOAc 3/1) to yield 2-chloro-4-(2-formyl-1-pyrrolyl)benzoic acid methyl ester (0.41 g). ESMS: 264 (MH^+).

2) The product obtained above was hydrolyzed with LiOH to give the title compound. ESMS: m/z 248 $(M-H)^-$.

Reference Example 35: 2-Chloro-4-[N-methyl-N-(methylsulfonyl)amino]benzoic acid.

1) A solution of di-tert-butyl dicarbonate (1.39 g) in dioxane (15 mL) was added dropwise to an ice-cold solution of 4-amino-2-chlorobenzoic acid (1.0 g) in 1 N NaOH (12.8 mL). The mixture was allowed to warm to room temperature and stirred overnight. Dioxane was removed and the aqueous solution was extracted with Et_2O. The aqueous solution was acidified with 1 N HCl to pH ~2. The precipitated solid was collected by filtration, washed with 1 N HCl and water, and dried under vacuum to yield 4-(tert-butoxycarbonylamino)-2-chlorobenzoic acid (1.13 g). ESMS: m/z 294 (MH^+).

2) NaOMe (0.16 g) was added to a solution of the product obtained above (0.36 g) in DMF (10 mL) under N_2. The mixture was cooled to 0 °C, and MeI (0.5 mL) was added. The mixture was stirred overnight at room temperature. NaOMe (0.14 g) and MeI (0.55 mL) were added and the mixture stirred for 6 h. THF was removed and the residue was partitioned between EtOAc and water. The EtOAc layer was separated and the aqueous layer was extracted with EtOAc. The combined EtOAc extract was washed with brine, dried $(MgSO_4)$, filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane/EtOAc 1/1) to yield 2-chloro-4-[N-methyl-N-(tert-butoxycarbonyl)amino]benzoic acid methyl ester (0.38 g). ESMS: m/z 322 $(M+Na)^+$.

3) A solution of the product obtained above in CH_2Cl_2 (10 mL) was treated with TFA (5 mL) for 2 h. The mixture was evaporated and the residue was taken up with EtOAc.

The EtOAc solution was washed successively with 10% Na_2CO_3 and brine, dried ($MgSO_4$), filtered and evaporated to give 0.25 g 2-chloro-4-(methylamino)benzoic acid methyl ester. ESMS: m/z 200 (MH^+).

4) Methanesulfonyl chloride (0.2 mL) was added under N_2 to a solution of the product obtained above (0.25 g) and pyridine (0.2 mL) in CH_2Cl_2 (20 mL) and the mixture was heated at 40 °C for 4 h. Pyridine (0.2 mL) and methanesulfonyl chloride (0.2 mL) were added and the mixture was heated for 2 h. The mixture was diluted with CH_2Cl_2 and the solution was washed with 1 N HCl and water, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: hexane/EtOAc 3/1-1/1) to give 2-chloro-4-[N-methyl-N-(methanesulfonyl)amino]benzoic acid methyl ester (0.26 g). ESMS: m/z 278 (MH^+).

5) The product obtained above was hydrolyzed with LiOH to give the title compound. ESMS: m/z 264 (MH^+).

Reference Example 36: 2-Chloro-4-thioureidobenzoic acid.

1) Benzoyl thiocyanate was generated by refluxing a solution of benzoyl chloride (0.31 mL) and ammonium thiocyanate (0.20 g) in acetone (15 mL) for 30 min. To this solution was added a solution of 4-amino-2-chlorobenzoic acid methyl ester (0.5 g) in CH_3CN (10 mL) and the mixture was refluxed for 5 h. The solvent was removed and the residue was partitioned between CH_2Cl_2 and water. The organic layer was separated, washed with brine, dried and evaporated. The residue was purified by column chromatography to yield 2-chloro-4-(3-benzoylthioureido)benzoic acid methyl ester (0.71 g). ESMS: 349 (MH^+).

2) The product obtained above was hydrolyzed with LiOH to give the title compound. ESMS: m/z 231(MH^+).

Reference Example 37: 2,6-Dichloro-4-phenyl benzoic acid.

1) To a solution of 2,6-dichloro-4-bromobenzoic acid methyl ester (0.55 g) in THF (10 mL) was added benzeneboronic acid (1.30 g), $Pd(PPh_3)_4$ (0.16 g) and 2M Na_2CO_3 (5 mL). The mixture was refluxed for 4 h under N_2. After cooling, the mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by preparative TLC (silica gel; eluent: hexane to EtOAc/hexane 1/1) to yield crude 2,6-dichloro-4-phenylbenzoic acid methyl ester (0.57 g). ESMS: m/z 281 (MH^+).

2) The product obtained above was hydrolyzed with LiOH to give the title compound. ESMS: m/z 267 (MH^+), 265 $(M-H)^-$.

Reference Example 38: 2,6-Dichloro-4-[2-(N-methyl)pyrrolyl] benzoic acid (*J. Med. Chem.* **41**, 2019 (1998))

1) 2,6-Dichloro-4-[2-(N-tert-butoxycarbonyl)pyrrolyl]-benzoic acid methyl ester was obtained in a similar manner as described in Reference Example 37-1) by replacing benzeneboronic acid with 2-(N-tert-butoxycarbonyl)pyrroleboronic acid.

2) To a solution of the product obtained above in CH_2Cl_2 (5 mL) was added TFA (5 mL). After 2 h under N_2, the mixture was diluted with CH_2Cl_2, washed with water and brine, dried (Na_2SO_4), filtered, and concentrated to give 2,6-dichloro-4-(2-pyrrolyl)benzoic acid methyl ester.

3) To a solution of the product obtained above(0.20 g) in THF (5 mL) were added NaH (0.07g) and MeI (0.14 mL). After stirring 2 h at room temperature, the mixture was diluted with EtOAc and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The residue was purified by preparative TLC (silica gel; eluent: EtOAc/hexane 1/10) to yield 2,6-

dichloro-4-[2-(N-methyl)pyrrolyl]benzoic acid methyl ester (0.088 g).

4) The product obtained above was hydrolyzed with LiOH to give the title compound.

Reference Example 39: 3-Bromo-2,6-dichlorobenzoic acid.

1) To a solution of 2,6-dichloro-4-aminobenzoic acid methyl ester (2.80 g) in CH_2Cl_2 (20 mL) at -10 °C was added a solution of tetrabutylammonium tribromide (6.94 g) in CH_2Cl_2 (30 mL) dropwise at -10 °C. After 2 h, the mixture was warmed to room temperature, washed with satd. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel; eluent: EtOAc/hexane 1:4) to yield 2,6-dichloro-3-bromo-4-aminobenzoic acid methyl ester (2.99 g). ESMS: m/z 298 (MH^+).

2) To a mixture of the product obtained above (2.99 g) in H_2SO_4 (10 mL) and water (20 mL) at 0 °C was added $NaNO_2$ (0.73 g). After 15 min, the mixture was treated with H_3PO_2. After 60 min, the mixture was extracted with EtOAc. The extract was washed with satd. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (silica gel; eluent: hexane to EtOAc/hexane 1:10) to yield 2,6-dichloro-3-bromobenzoic acid methyl ester (2.11 g). ESMS: m/z 282 (MH^+).

3) The product obtained above was hydrolyzed with LiOH to give the title compound. ESMS: m/z 268 (MH^+) and 266 (M^- - 1).

Reference Example 40: 2-Chloro-4-(tert-butoxycarbonyl)benzoic acid

1) 3-Chloro-4-methoxycarbonylbenzoic acid (0.24 g) was dissolved in DMF (2.5 mL) under N_2 then CDI (0.36 g) was

added and the resulting mixture was stirred at 40 °C for 2h. *t*-BuOH (0.54 mL) and DBU (0.33 mL) were added and the resulting mixture was stirred at 40 °C for 2 days. The mixture was evaporated and the residue was taken up with AcOEt, washed with 1N HCl and sat. $NaHCO_3$, dried ($MgSO_4$), filtered and evaporated. The residue was purified by column chromatography (silica gel; eluent: toluene) to give 2-chloro-4-(tert-butoxycarbonyl)benzoic acid methyl ester (216 mg).

2) The product obtained above was hydrolyzed with LiOH to give the title compound.

Reference Example 41: 4-(N,N-Dimethylsulfamoyl)amino-2-chlorobenzoic acid

1) Pyridine (0.4 mL) was added to a solution of methyl 4-amino-2-chlorobenzoate (0.3 g) in CH_2Cl_2 (10 mL) at 0 °C under N_2. N,N-Dimethylsulfamoyl chloride (0.21 mL) was added and the mixture was stirred at room temperature for 16 hours and refluxed for 5 hours. DMAP (0.4 g) was added and the mixture was stirred for 3 hours. The mixture was diluted with CH_2Cl_2 (100 mL), washed successively with 1N HCl, brine, satd. $NaHCO_3$ and brine, dried and evaporated. The residue was purified by flash column chromatography (silica gel; eluent: EtOAc/hexane 1:3) to give 0.31 g of methyl 4-(N,N-dimethylsulfamoyl)amino-2-chlorobenzoate. ESMS: m/z 293 (MH^+)

2) The product obtained above was hydrolyzed with LiOH in a similar manner as described in Example 1-5) to give the title compound. ESMS: m/z 279 (MH^+)

Reference Example 42: Trimethyl-(2-cyano-3-thienyl)tin

A mixture of 3-bromothiophene-2-carbonitrile (385 mg), hexamethylditin (615 mg) and $Pd(PPh_3)_4$ (116mg) in toluene (8 mL) was stirred at 130 °C under N_2 for 16 h. The organic

solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (silica gel; eluent: AcOEt-hexane 1 : 20) to give the title compound (406 mg).

Reference Example 43: 2,6-Di(methoxymethoxy)benzeneboronic acid

1) DIEA (26 mL) and methoxymethoxy chloride (8.20 mL) were added to a suspension of resorcinol (3.65 g) in CH_2Cl_2 (40 mL) under N_2 at 0°C. The mixture was stirred at the same temperature for 10 min and stirred at room temperature for 16 hours. DIEA (13 mL) and methoxymethoxy chloride (4 mL) were added to the mixture and the mixture was stirred for 1 hour. The mixture was added to water and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and evaporated, and the residue was purified by flash column chromatography (silica gel; eluent: EtOAc/hexane 15%) to give 1,3-di(methoxymethoxy)benzene (2.44 g).

2) The product obtained above was treated in a similar procedure as described in Example 7-1) to give the title compound.

RPMI-CS-1 Cell Adhesion Assay:

The following assay established the activity of the present compounds in inhibiting β_7-mediated cell adhesion in a representative *in vitro* system. This assay measures the adhesive interactions of a B-cell line, RPMI, known to express $\alpha_4\beta_7$ (Erle et al., *J. Immunol.* 153: 517-528 (1994)), to the alternatively spliced region of fibronectin referred to as CS-1, in the presence of test compounds. The test compounds were added in increasing concentrations to RPMI cells and then the cell-compound mixture was added to CS-1 coated microwells. The plates were incubated, washed and the percentage of attached cells were

quantitated. The present assay directly demonstrates the cell adhesion inhibitory activity and adhesion modulatory activity of the present compounds.

RPMI-CS-1 assay

The CS-1 derived peptide, CLHPGEILDVPST, and the scrambled control peptide, CLHGPIELVSDPT, were synthesized at Tanabe Research Laboratories, USA, Inc. on a Beckman 990 synthesizer using t-Boc methodology. The peptides were immobilized onto microtiter plates using the heterobifunctional crosslinker 3-(2-pyridyldithio)propionic acid N-hydroxysuccinimide ester (SPDP) as reported (Pierschbacher, et al., *Proc. Natl. Acad. Sci. USA* 80: 1224-1227 (1983)). Microtiter plates were coated with 20 µg/ml human serum albumin (HSA) for 2 hours at room temperature, washed once with PBS and derivatized with 10 µg/ml SPDP for 1 hour. After washing, 100 µl of a 100 µg/ml cysteine containing peptide solution which had been recently dissolved was added to the wells and allowed to crosslink to the plates overnight at 4 °C. Unbound peptide was removed from the plates by washing with PBS. To block non-reacted sites, the plates were coated with 100 µl of a 2.5 mg/ml BSA solution in PBS for one hour at 37° C. 100 µl of RPMI cells (2.5×10^6 cells/ml) in Dulbecco's Modified Eagles Medium (DMEM) plus 0.25 % ovalbumin were added to peptide coated dishes and incubated for 1 hour at 37 °C. Following this incubation, the plates were washed with PBS three times using an EL404 plate washer and the number of adherent cells was quantitated by measuring enzymatic activity of endogenous N-acetyl-hexosaminidase (Landegren, *J. Immunol. Methods*, 67: 379-388 (1984)). To do this, the enzyme substrate p-nitrophenyl-N-acetyl-β-D-glucoseaminide is dissolved at 7.5 mM in 0.1 M citrate buffer pH 5 and then mixed with an equal volume of 0.5% Triton X100. 50 µl of the substrate solution was added to the plates and the plates were incubated at 37 °C for 60 minutes. The reaction was stopped by the addition of 100 µl

50 mM glycine, 5 mM EDTA buffer pH 10.4. The amount of liberated p-nitrophenol was quantitated by reading the optical density at 405 nm using a vertical pathway spectrophotometer to quantitate attachment (VMAX Kinetic Microplate Reader, Molecular Devices, Menlo Park, CA). This procedure is a modification of a previously published method (Cardarelli et al., *J. Biol. Chem.* 269: 18668-18673 (1994)).

In this assay, IC_{50} value ranges (μM) are depicted by A, B, C and D. These ranges as follows.

$D > 5 \geq C > 1 \geq B > 0.3 \geq A$

The following TABLE 31 illustrates the IC_{50} values for selected compounds of the present invention in the RPMI-CS-1 assay. The ranges are as described above.

TABLE 31

Example Number	RPMI-CS-1
1A	B
1B	A
2	C
3	A
4A	C
4B	B
5	C
6	D
7A	A
7B	A
8	A
9	A
10	A
11	A
12	A
13	A
14	A

15	B
16	A
17	A
18	B
19	C
20	A
21	A
22	C
23	B
24	A
25	B
26	B
27	A
28	B
29	C
30	B
31	A
32	A
33	B
34	C
35	C
36	A
37	B
38	B
39	B
40	B
41	C
42	B
43	C
44	B
45	A
46	A
47	A
48	C
49	B
50	A
51	B
52	D
53	C
54	B

55	C
56	B
57	C
58	B
59	C
60	B
61	D
62	A
63	B
64	A
65	A
66	A
67	B
68	A
69	A
70	A
71	A
72	B
73	A
74	B
75	A
76	D
77	A
78	B
79	A
80	A
81	D
82	D
83	B
84	C
85	B
86	A
87	B
88	C
89	B
90	B
91	C
92	C
93	D
94	C

95	C
96	B
97	B
100	C
101	D
102	D
103	D
104	D
105	D
106	C
107	C
108	C
109	D
110	D
111	C
112	B
113	A
114	B
115	C
116	C
117	C
118	C
119	D
120	D
121	C
122	C
123	C
124	C
125	C
126	C
127	D
128	B
129	C
130	D
131	A
132	A
133	A
134	A
135	A
136	B

137	B
138	A
139	A
140	B
141	B
142	A
143	A
144	A
145	C
146	B
147	A
148	A
149	A
150	A
151	A
152A	A
152B	A
152C	B
153A	A
153B	A
154	A
155	A
156	A
157	A
158	A
159	A
160	A
161	A
162	A
163	A
164	A
165	A
166	A
167	A
168	A
169	A
170	A
171	A
172	A
173	A

174	A
175	A
176	B
177	A
178	A
179	A
180	A
181	B
182	A
183	A
184	A
186	B
187	A
188	A
189	A
190	A
191	A
192	A
193	A
194	C
195	B
196	A
197	B
198	A
199	A
200	A
201	A
202	A
203	A
204	A
205	A
206	A
207	A
208	A
209	A
210	C
211	A
212	C
213	C
214	B

215	B
216	C
217	C
218	C
219	B
220	A
221	C
222	A
223	A
224	C
225	C
226	A
227	A
228	A
229	A
230	B
231	A
232	A
233	B
234	A
235	A
236	A
237	A
238	A
239	A
240	A
241	A
242	A
243	A
244	A
245	A
246	A
247	A
248	A
250	A
251	A
252	A
253	A
254	A
255	A

256	A
257	A
258	A
259	A
262	A
263A	A
263B	A
264	A
265	A
266	A
267	D
268	C
269	D
270	A
271	A
272	B
273	C
274	C
275	D
276	D
277	A
278	A
279	A
280	A
281	C
282	C
283	C
284	C
285	A
286	A
287	B
288	C
289	B
290	C
291	C
292	C
293	C
294	C
295	C
296	A

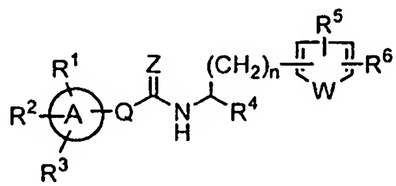
297	A
298	A
299	A
300	B
301	A
302	A
303	A
304	A
305	B
306	A
307	A
308	A
309	A
310	A
311	A
312	A
316	A
317	A
319	A
320	A
321	A
322	A
323	A
324	A
325	A
326	A
327	A
328	A
329	C
331	A
332	B
333	A
334	A
335	B
336	A
337	A
338	A
339	A
340	A
341	A

342	A
343	C
344	C
345	B
346	A
347	A
348	A
349	A
350	A
351	A
352	B
353	A
354	A
355	A
356	A

CLAIMS

What is claimed is:

1. A compound of the formula [I]:



[I]

wherein

Ring A is an aromatic hydrocarbon ring or a heterocyclic ring;

Q is a bond, a carbonyl group, a lower alkylene group which may be substituted by a hydroxyl group or phenyl group, a lower alkenylene group, or a -O-(lower alkylene)-group;

n is an integer of 0, 1 or 2;

W is oxygen atom, sulfur atom, a -CH=CH- group or a -N=CH- group;

Z is oxygen atom or sulfur atom;

R^1, R^2 and R^3 are the same or different and are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a substituted or unsubstituted lower alkyl group,

d) a substituted or unsubstituted lower alkoxy group,

e) a nitro group,

f) a substituted or unsubstituted amino group,

g) a carboxyl group or an amide or an ester thereof,

h) a cyano group,

i) a lower alkylthio group,

j) a lower alkanesulfonyl group,

k) a substituted or unsubstituted sulfamoyl group,

l) a substituted or unsubstituted aryl group,

m) a substituted or unsubstituted heterocyclic group, and

n) hydroxyl group,

or two of R^1, R^2 and R^3 may combine each other at the terminal thereof to form a lower alkylenedioxy group;

R^4 is tetrazolyl group, a carboxyl group, or an amide or an ester thereof;

R^5 is a group selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) a substituted or unsubstituted amino group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a substituted or unsubstituted lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom, and

i) 2-oxopyrrolidinyl group;

R^6 is a group selected from the group consisting of :

a) a substituted or unsubstituted phenyl group, and

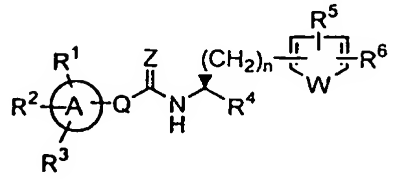
b) a substituted or unsubstituted heteroaryl group;

with the proviso that

when Ring A is a benzene ring, the ring is not substituted with methyl group in the 3- and the 5-positions or in the 2- and the 4-positions;

or a pharmaceutically acceptable salt thereof.

2. The compound according to claim 1, wherein the chemical structure is formula [I-A]:

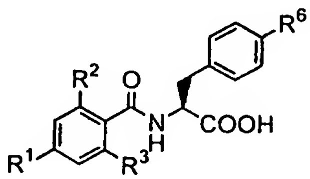


[I-A]

wherein symbols are the same as defined above.

3. The compound according to claim 1, with the additional proviso that when Ring A is a benzene ring, the ring is substituted in at least one of 2- and 6-positions.

4. The compound according to claim 1, wherein the chemical structure is formula [I-B]:



[I-B]

wherein symbols are the same as defined above.

5. The compound according to claim 4, wherein

R^1 is hydrogen atom, a halogen atom, carboxyl group, carbamoyl group, nitro group, a substituted or unsubstituted amino group, a substituted or unsubstituted heterocyclic ring;

R^2 is hydrogen atom, a lower alkyl group or a halogen atom;

R^3 is hydrogen atom, a lower alkyl group or a halogen atom;

R^6 is a phenyl group which may be substituted at 2-, 4-, and/or 6-position of the phenyl group by a group selected from the group consisting of:

1) a halogen atom,

2) a substituted or unsubstituted lower alkoxy group,

3) a substituted or unsubstituted lower alkyl group ,

4) a substituted or unsubstituted amino group,

5) a substituted or unsubstituted carbamoyl group, and

6) a substituted or unsubstituted sulfamoyl group.

6. The compound according to claim 1, wherein

Ring A is a benzene ring, a pyridine ring, a pyrazine ring, a furan ring, an isoxazole ring, a benzofuran ring, a thiophene ring, a pyrrole ring, or an indole ring;

R^1, R^2 and R^3 are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a lower alkyl group which may be substituted by a halogen atom or a (halogenobenzoyl)amino group,

d) a lower alkoxy group which may be substituted by a halogen atom,

e) a nitro group,

f) an amino group which may be substituted by 1-2 groups selected from the group consisting of 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a halogenobenzoyl group, 4) a lower alkoxycarbonyl group, 5) a lower alkanesulfonyl group which may be substituted by a halogen atom, 6) a benzenesulfonyl group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 7) thiophenesulfonyl group, 8) a carbamoyl group which may be substituted by a lower alkyl group, a lower alkyl-phenyl group, 9) a thiocarbamoyl group which may be substituted by a lower alkyl group, phenyl group, a phenyl-lower alkyl group, 10) thiazolinyl group, and 11) a sulfamoyl group which may be substituted by a lower alkyl group;

g) a carboxyl group,

h) a carbamoyl group which may be substituted by a lower alkanesulfonyl group,

i) a lower alkoxycarbonyl group,

j) a cyano group,

k) a lower alkylthio group,

l) a lower alkanesulfonyl group,

m) a sulfamoyl group,

n) a phenyl group,

o) a pyrrolidinyl group which may be substituted by oxo group,

p) a pyrrolyl group which may be substituted by a group selected from the group consisting of 1) a lower alkanoyl group which may be substituted by a halogen atom, 2) a halogen atom, 3) formyl group, and 4) a lower alkyl group which may be substituted by hydroxy group,

q) a thienyl group,

r) an isoxazolyl group which may be substituted by a lower alkyl group,

s) a thiazolyl group,

t) a pyrazolyl group,

u) a pyrazinyl group,

v) a pyridyl group, and

w) hydroxyl group;

R^4 is selected from the group consisting of:

a) carboxyl group,

b) a lower alkoxycarbonyl group which may be substituted by 1) pyridyl group or 2) an amino group which may be substituted by a lower alkyl group,

c) a lower cycloalkoxy carbonyl group,

d) a carbamoyl group which may be substituted by a hydroxy group or a lower alkanesulfonyl group, and

e) a tetrazolyl group;

R^5 is selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) an amino group which may be substituted by a lower alkanoyl group, a lower alkoxycarbonyl group or a lower alkanesulfonyl group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a lower alkyl group which may be substituted by 1) hydroxyl group, or 2) an imino group which is substituted by hydroxyl group or a lower alkoxy group,

g) a lower alkoxy group,

h) a halogen atom, and

i) 2-oxopyrrolidinyl group;

R^6 is the group selected from the group consisting of:

a) a phenyl group which may have 1-5 substituents selected from the group consisting of:

1) a halogen atom,

2) a nitro group,

3) a formyl group,

4) a hydroxyl group,

5) a carboxyl group,

6) a lower alkoxy group which may be substituted by a group selected from the group consisting of i) a carboxyl group or an amide or an ester thereof, ii) hydroxyl group, iii) a cyano group, iv) a halogen atom, v) an amino group which may be substituted by a lower alkyl group, vi) a pyridyl group, vii) a thiazolyl group which may be substituted by a lower alkyl group, viii) an isoxazolyl group which may be substituted by a lower alkyl group, ix) a piperidyl group which may be substituted by a lower alkyl group, x) a pyrrolidinyl group which may be substituted by a lower alkyl group, xi) a phenyl group which may be substituted by a halogen atom, xii) a furyl group, xiii) a thienyl group, and xiv) a lower alkoxy group

7) a lower alkyl group which may be substituted by a group selected from the group consisting of i) a halogen atom, ii) hydroxyl group, iii) carboxyl group or an amide or an ester thereof, iv) a lower alkoxy group, v) an amino group which may be substituted by 1-2 groups selected from the group consisting of a

lower alkyl group, a hydroxy-lower alkyl group, a (lower alkylamino)-lower alkyl group, phenyl-lower alkyl group, a phenyl group, and a pyridyl group, vi) a piperidinyl group which may be substituted by a lower alkylenedioxy group, an oxo group or a hydroxy group, vii) a morpholino group which may be substituted by a lower alkyl group, viii) thiomorpholino group which may be oxidized, ix) piperazinyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a lower alkanoyl group or a phenyl-lower alkyl group, x) pyrrolidinyl group, which may be substituted by one group, and xi) an imidazolidinyl group which may be substituted by 1-3 groups selected from the group consisting of a lower alkyl group and oxo group,

8) a lower alkenyl group which may be substituted by carboxyl group or an amide or an ester thereof,

9) an amino group which may be substituted by a group selected from the group consisting of i) a phenyl group, ii) a lower alkoxycarbonyl group, iii) a lower alkanesulfonyl group, iv) a carbamoyl group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, v) a lower alkanoyl group, vi) a lower alkyl group, vii) a lower alkenyl group, and viii) a thiocarbamoyl group which may be substituted by a lower alkyl group,

10) a carbamoyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a morpholino-lower alkyl group, a phenyl-lower alkyl group or a lower alkanesulfonyl group,

11) a sulfamoyl group which may be substituted by a group consisting of i) a lower alkyl group, ii) a benzoyl group, iii) a lower alkoxycarbonyl group, and iv) a lower alkanoyl group,

12) a lower alkenyloxy group,

13) a lower alkylenedioxy group,

14) a piperazinylcarbonyl group which may be substituted by a lower alkyl group,

15) a lower alkanoyl group,

16) cyano group,

17) a lower alkylthio group,

18) a lower alkanesulfonyl group,

19) a lower alkylsulfinyl group, and

20) a group of the formula: $-(CH_2)_q-O-$ wherein q is an integer of 2 or 3;

b) a pyridyl group which may be substituted by a lower alkyl group;

c) a thienyl group which may be substituted by a group selected from the group consisting of:

1) a halogen atom,

2) a lower alkyl group which may be substituted by hydroxyl group,

3) cyano group,

4) formyl group,

5) a lower alkoxy group, and

6) a lower alkanoyl group;

d) a benzofuranyl group;

e) a pyrimidinyl group which may be substituted by a lower alkoxy group;

f) an isoxazolyl group which may be substituted by a lower alkyl group; and

g) a pyrrolyl group which may be substituted by a lower alkoxycarbonyl group.

7. The compound according to claim 6, wherein

Ring A is a benzene ring,

Q is a bond,

W is a -CH=CH- group,

R^1 is selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a lower alkyl group,

d) a lower alkoxy group,

e) nitro group,

f) an amino group which may be substituted by a group selected from the group consisting of 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a lower alkoxycarbonyl group, 4) a lower alkanesulfonyl group which may be substituted by a halogen atom, 5) a benzenesulfonyl group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 6) thiophenesulfonyl group, 7) a carbamoyl group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, 8) a thiocarbamoyl group which may be substituted by a lower alkyl group, and 9) a sulfamoyl group which may be substituted by a lower alkyl group,

g) carboxyl group

h) a carbamoyl group which may be substituted by a lower alkanesulfonyl group,

i) a lower alkanesulfonyl group,

j) a sulfamoyl group,

k) phenyl group,

l) a pyrrolidinyl group which may be substituted by oxo group,

l) a pyrrolyl group which may be substituted by a lower alkyl group,

m) a thienyl group,

n) an isoxazolyl group which may be substituted by a lower alkyl group,

o) a thiazolyl group

p) a pyrazolyl group,

q) a pyrazinyl group,

r) a pyridyl group, and

s) a hydroxyl group;

R^2 is hydrogen atom, or a halogen atom;

R^3 is hydrogen atom, or a halogen atom;

R^4 is a) a carboxyl group,

b) a lower alkoxycarbonyl group which may be substituted by a lower alkyl-amino group, or

c) a carbamoyl group which may be substituted by a lower alkanesulfonyl group;

R^5 is selected from the group consisting of:

a) hydrogen atom,

b) an amino group which may be substituted by a lower alkanoyl group, a lower alkoxycarbonyl group or a lower alkanesulfonyl group,

c) a lower alkanoyl group,

d) a lower alkyl group which may be substituted by 1) hydroxyl group, or 2) an imino group which is substituted by hydroxyl group or a lower alkoxy group,

e) a lower alkoxy group, and

f) a halogen atom;

R^6 is a phenyl group which may have 1-5 substituents selected from the group consisting of:

a) a halogen atom,

b) a formyl group,

c) a hydroxyl group,

d) a lower alkoxy group which may be substituted by 1) a carboxyl group, 2) a hydroxyl group, 3) a cyano group, 4) a halogen atom, 5) an amino group which may be substituted by a lower alkyl group, 6) a pyridyl group, 7) a phenyl group, 8) a thienyl group, or 9) a lower alkoxy group,

e) a lower alkyl group which may be substituted by 1) an amino group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a (lower alkylamino)-lower alkyl group or a phenyl group, 2) a piperidinyl group

which may be substituted by a lower alkylenedioxy group, 3) a morpholino group which may be substituted by a lower alkyl group, 4) a thiomorpholino group in which sulfur atom may be oxidized, 5) a piperazinyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a lower alkanoyl group or a phenyl-lower alkyl group, 6) pyrrolidinyl group, which may be substituted by oxo group, or 7) an imidazolidinyl group which may be substituted by 1-3 groups selected from the group consisting of a lower alkyl group and oxo group,

f) an amino group which may be substituted by 1) a lower alkoxycarbonyl group, 2) a lower alkanesulfonyl group, 3) a carbamoyl group which may be substituted by a lower alkyl group a lower alkyl-phenyl group, 4) a lower alkanoyl group, 5) a lower alkyl group, 6) a lower alkenyl group, or 7) a thiocarbamoyl group which may be substituted by a lower alkyl group,

g) a carbamoyl group which may be substituted by 1) a lower alkyl group, 2) a hydroxy-lower alkyl group, 3) a morpholino-lower alkyl group, 4) a phenyl-lower alkyl group, or 5) a lower alkanesulfonyl group,

h) a sulfamoyl group which may be substituted by a lower alkyl group,

i) a lower alkenyloxy group,

j) a lower alkylenedioxy group,

k) a cyano group,

l) a lower alkylthio group, and

m) a lower alkanesulfonyl group.

8. The compound according to claim 5 or 7, wherein R^1 is 1) hydrogen atom, 2) a halogen atom, 3) a lower alkanoylamino group, 4) a lower alkoxycarbonylamino group, 5) a lower alkanesulfonylamino group which may be substituted by a halogen atom, 6) a benzenesulfonylamino group which may be substituted by a lower alkyl group, a

trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 7) thiophenesulfonylamino group, 8) an ureido group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, 9) a lower alkyl-thioureido group, or 10) a lower alkylsulfamoylamino group, R^2 is a halogen atom, R^3 is hydrogen atom or a halogen atom, and R^6 is a phenyl group which may have 1-3 substituents selected from the group consisting of 1) a lower alkoxy group, 2) a lower alkyl group which may be substituted by a group selected from the group consisting of a lower alkylamino group, a hydroxy-lower alkylamino group, a lower alkylamino-lower alkylamino group, piperidinyl group, a lower alkyl-piperidinyl group, morpholino group, a lower alkyl-morpholino group, a thiomorpholino group, piperazinyl group, a lower alkyl-piperazinyl group, a lower alkanoyl-piperazinyl group, and a pyrrolidinyl group, 3) a sulfamoyl group which may be substituted by a lower alkyl group, 4) a carbamoyl group which may be substituted by a lower alkyl group.

9. The compound according to claim 8, wherein R^1 is hydrogen atom, R^3 is a halogen atom, and R^6 is 2-(lower alkoxy)phenyl group, 2,6-di(lower alkoxy)phenyl group, 2,6-di(lower alkoxy)-4-[[N,N-di(lower alkyl)amino]lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[(4-lower alkyl-1-piperazinyl)lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[1-piperidinyl-lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[N,N-di(lower alkyl)carbamoyl]phenyl group or 2,6-di(lower alkoxy)-4-[(morpholino)lower alkyl]phenyl group.

10. The compound according to claim 9, wherein a lower alkoxy group is methoxy group.

11.

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(piperidinomethyl)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-methylpiperazinyl)amino]phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N,N-dimethylamino)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N,N-dimethylcarbamoyl)phenyl]-L-phenylalanine;

N-(2,6-dichloro-4-hydroxybenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2-ethoxy-6-methoxyphenyl)-L-phenylalanine;

N-(2,6-difluorobenzoyl)-4-(2-6,dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2,3-methylenedioxy-6-methoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethy)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2,4,6-trimethoxyphenyl)-L-phenylalanine;

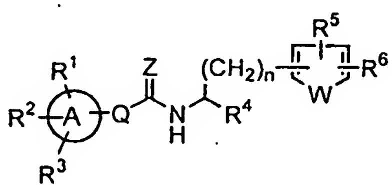
N-[2,6-dichloro-4-[(trifluoromethanesulfonyl)amino]-benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine; or

N-[2,6-dichloro-4-[(2-thienylsulfonyl)amino]benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

or a lower alkyl ester thereof;

or pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition which comprises a therapeutically effective amount of a compound of the formula [I]:



[I]

wherein

Ring A is an aromatic hydrocarbon ring or a heterocyclic ring;

Q is a bond, a carbonyl group, a lower alkylene group which may be substituted by a hydroxyl group or phenyl group, a lower alkenylene group, or a -O-(lower alkylene)-group;

n is an integer of 0, 1 or 2;

W is oxygen atom, sulfur atom, a -CH=CH- group or a -N=CH- group;

Z is oxygen atom or sulfur atom;

R^1, R^2 and R^3 are the same or different and are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a substituted or unsubstituted lower alkyl group,

d) a substituted or unsubstituted lower alkoxy group,

e) a nitro group,

f) a substituted or unsubstituted amino group,

g) a carboxyl group or an amide or an ester thereof,

h) a cyano group,

i) a lower alkylthio group,

j) a lower alkanesulfonyl group,

k) a substituted or unsubstituted sulfamoyl group,

l) a substituted or unsubstituted aryl group,

m) a substituted or unsubstituted heterocyclic group, and

n) hydroxyl group;

or two of R^1, R^2 and R^3 may combine each other at the terminal thereof to form a lower alkylenedioxy group;

R^4 is tetrazolyl group, a carboxyl group, or an amide or an ester thereof;

R^5 is a group selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) a substituted or unsubstituted amino group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a substituted or unsubstituted lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom,

i) 2-oxopyrrolidinyl group;

R^6 is a group selected from the group consisting of :

a) a substituted or unsubstituted phenyl group,

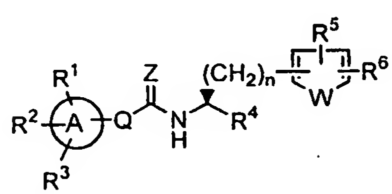
b) a substituted or unsubstituted pyridyl group, and

c) a substituted or unsubstituted heteroaryl group;

or a pharmaceutically acceptable salt thereof;

and a pharmaceutically acceptable carrier or diluent.

13. The pharmaceutical composition according to claim 12, wherein the chemical structure is formula [I-A]:



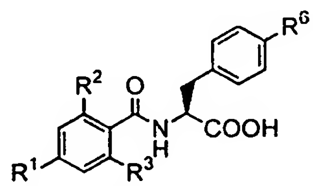
[I-A]

wherein symbols are the same as defined above.

14. The pharmaceutical composition according to claim 12, with the proviso that when Ring A is a benzene ring, the ring is not substituted with methyl group in the 3- and the 5-positions or in the 2- and the 4-positions.

15. The pharmaceutical composition according to claim 12, with the additional proviso that when Ring A is a benzene ring, the ring is substituted in at least one of 2- and 6-positions.

16. The pharmaceutical composition according to claim 12, wherein the chemical structure is formula [I-B]:



[I-B]

wherein symbols are the same as defined above.

17. The pharmaceutical composition according to claim 16, wherein

R^1 is hydrogen atom, a halogen atom, carboxyl group, carbamoyl group, nitro group, a substituted or unsubstituted amino group, a substituted or unsubstituted heterocyclic ring;

R^2 is hydrogen atom, a lower alkyl group or a halogen atom;

R^3 is hydrogen atom, a lower alkyl group or a halogen atom;

R^6 is a phenyl group which may be substituted at 2-, 4-, and/or 6-position of the phenyl group by a group selected from the group consisting of:

1) a halogen atom,

2) a substituted or unsubstituted lower alkoxy group,

3) a substituted or unsubstituted lower alkyl group ,

4) a substituted or unsubstituted amino group,

5) a substituted or unsubstituted carbamoyl group, and

6) a substituted or unsubstituted sulfamoyl group.

18. The pharmaceutical composition according to claim 12, wherein

Ring A is a benzene ring, a pyridine ring, a pyrazine ring, a furan ring, an isoxazole ring, a benzofuran ring, a thiophene ring, a pyrrole ring, or an indole ring;

R^1, R^2 and R^3 are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a lower alkyl group which may be substituted by a halogen atom or a (halogenobenzoyl)amino group,

d) a lower alkoxy group which may be substituted by a halogen atom,

e) a nitro group,

f) an amino group which may be substituted by 1-2 groups selected from the group consisting of 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a halogenobenzoyl group, 4) a lower alkoxycarbonyl group, 5) a lower alkanesulfonyl group which may be substituted by a halogen atom, 6) a benzenesulfonyl group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 7) thiophenesulfonyl group, 8) a carbamoyl group which may be substituted by a lower alkyl group, a lower alkyl-phenyl group, 9) a thiocarbamoyl group which may be substituted by a lower alkyl group, phenyl group, a phenyl-lower alkyl group, 10) thiazolynyl group, and 11) a sulfamoyl group which may be substituted by a lower alkyl group;

g) a carboxyl group,

h) a carbamoyl group which may be substituted by a lower alkanesulfonyl group,

i) a lower alkoxycarbonyl group,

j) a cyano group,

k) a lower alkylthio group,

l) a lower alkanesulfonyl group,

m) a sulfamoyl group,

n) a phenyl group,

o) a pyrrolidinyl group which may be substituted by oxo group,

p) a pyrrolyl group which may be substituted by a group selected from the group consisting of 1) a lower alkanoyl group which may be substituted by a halogen atom, 2) a halogen atom, 3) formyl group, and 4) a lower alkyl group which may be substituted by hydroxy group,

q) a thienyl group,

r) a isoxazolyl group which may be substituted by a lower alkyl group,

s) a thiazolyl group,

t) a pyrazolyl group,

u) a pyrazinyl group,

v) a pyridyl group, and

w) hydroxyl group;

R^4 is selected from the group consisting of:

a) carboxyl group,

b) a lower alkoxycarbonyl group which may be substituted by 1) pyridyl group or 2) an amino group which may be substituted by a lower alkyl group,

c) a lower cycloalkoxycarbonyl group,

d) a carbamoyl group which may be substituted by a hydroxy group or a lower alkanesulfonyl group, and

e) a tetrazolyl group;

R^5 is selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) an amino group which may be substituted by a lower alkanoyl group, a lower alkoxycarbonyl group or a lower alkanesulfonyl group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a lower alkyl group which may be substituted by 1) hydroxyl group, or 2) an imino group which is substituted by hydroxyl group or a lower alkoxy group,

g) a lower alkoxy group,

h) a halogen atom,

i) 2-oxopyrrolidinyl group;

R^6 is the group selected from the group consisting of:

a) a phenyl group which may have 1-5 substituents selected from the group consisting of:

1) a halogen atom,

2) a nitro group,

3) a formyl group,

4) a hydroxyl group,

5) a carboxyl group,

6) a lower alkoxy group which may be substituted by a group selected from the group consisting of i) a carboxyl group or an amide or an ester thereof, ii) hydroxyl group, iii) a cyano group, iv) a halogen atom, v) an amino group which may be substituted by a lower alkyl group, vi) a pyridyl group, vii) a thiazolyl group which may be substituted by a lower alkyl group, viii) an isoxazolyl group which may be substituted by a lower alkyl group, ix) a piperidyl group which may be substituted by a lower alkyl group, x) a pyrrolidinyl group which may be substituted by a lower alkyl group, xi) a phenyl group which may be substituted by a halogen atom, xii) a furyl group, xiii) a thienyl group, and xiv) a lower alkoxy group

7) a lower alkyl group which may be substituted by a group selected from the group consisting of i) a halogen atom, ii) hydroxyl group, iii) carboxyl group or an amide or an ester thereof, iv) a lower alkoxy group, v) an amino group which may be substituted by 1-2 groups selected from the group consisting of a lower alkyl group, a hydroxy-lower alkyl group, a (lower alkylamino)-lower alkyl group, phenyl-lower alkyl group, a phenyl group, and a pyridyl group, vi) a piperidinyl group which may be substituted by a lower alkylenedioxy group, an oxo group or a hydroxy group, vii) a morpholino group which may be substituted by a lower alkyl group, viii) thiomorpholino group which may be oxidized, ix) piperazinyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a lower alkanoyl group or a phenyl-lower alkyl group, x) pyrrolidinyl group which may be substituted by oxo group, and xi) an imidazolidinyl group which may be substituted by 1-3 groups selected from the group consisting of lower alkyl group and oxo group,

8) a lower alkenyl group which may be substituted by carboxyl group or an amide or an ester thereof,

9) an amino group which may be substituted by a group selected from the group consisting of i) a phenyl group, ii) a lower alkoxycarbonyl group, iii) a lower alkanesulfonyl group, iv) a carbamoyl group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, v) a lower alkanoyl group, vi) a lower alkyl group, vii) a lower alkenyl group, and viii) a thiocarbamoyl group which may be substituted by a lower alkyl group,

10) a carbamoyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a

morpholino-lower alkyl group, a phenyl-lower alkyl group or a lower alkanesulfonyl group,

11) a sulfamoyl group which may be substituted by a group consisting of i) a lower alkyl group, ii) a benzoyl group, iii) a lower alkoxycarbonyl group, and iv) a lower alkanoyl group,

12) a lower alkenyloxy group,

13) a lower alkylenedioxy group,

14) a piperazinylcarbonyl group which may be substituted by a lower alkyl group,

15) a lower alkanoyl group,

16) cyano group,

17) a lower alkylthio group,

18) a lower alkanesulfonyl group,

19) a lower alkylsulfinyl group, and

20) a group of the formula: $-(CH_2)_q-O-$ wherein q is an integer of 2 or 3;

b) a pyridyl group which may be substituted by a lower alkyl group;

c) a thienyl group which may be substituted by a group selected from the group consisting of:

1) a halogen atom,

2) a lower alkyl group which may be substituted by hydroxyl group,

3) cyano group,

4) formyl group,

5) a lower alkoxy group, and

6) a lower alkanoyl group;

d) a benzofuranyl group;

e) a pyrimidinyl group which may be substituted by a lower alkoxy group;

f) an isoxazolyl group which may be substituted by a lower alkyl group, and

g) a pyrrolyl group which may be substituted by a lower alkoxycarbonyl group.

19. The pharmaceutical composition according to claim 18, wherein

Ring A is a benzene ring,

Q is a bond,

W is a -CH=CH- group,

R^1 is selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a lower alkyl group,

d) a lower alkoxy group,

e) nitro group,

f) an amino group which may be substituted by a group selected from the group consisting of 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a lower alkoxycarbonyl group, 4) a lower alkanesulfonyl group which may be substituted by a halogen atom, 5) a benzenesulfonyl group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 6) thiophenesulfonyl group, 7) a carbamoyl group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, 8) a thiocarbamoyl group which may be substituted by a lower alkyl group, and 9) a sulfamoyl group which may be substituted by a lower alkyl group,

g) carboxyl group

h) a carbamoyl group which may be substituted by a lower alkanesulfonyl group,

i) a lower alkanesulfonyl group,

j) a sulfamoyl group,

k) phenyl group,

l) a pyrrolidinyl group which may be substituted by oxo group,

l) a pyrrolyl group which may be substituted by a lower alkyl group,

m) a thienyl group,

n) an isoxazolyl group which may be substituted by a lower alkyl group,

o) a thiazolyl group

p) a pyrazolyl group,

q) a pyrazinyl group,

r) a pyridyl group, and

s) hydroxyl group;

R^2 is hydrogen atom, or a halogen atom;

R^3 is hydrogen atom, or a halogen atom;

R^4 is a) a carboxyl group,

b) a lower alkoxycarbonyl group which may be substituted by a lower alkyl-amino group, or

c) a carbamoyl group which may be substituted by a lower alkanesulfonyl group;

R^5 is selected from the group consisting of:

a) hydrogen atom,

b) an amino group which may be substituted by a lower alkanoyl group, a lower alkoxycarbonyl group or a lower alkanesulfonyl group,

c) a lower alkanoyl group,

d) a lower alkyl group which may be substituted by 1) hydroxyl group, or 2) an imino group which is substituted by hydroxyl group or a lower alkoxy group,

g) a lower alkoxy group, and

h) a halogen atom;

R^6 is a phenyl group which may have 1-5 substituents selected from the group consisting of:

a) a halogen atom,

b) a formyl group,

c) a hydroxyl group,

d) a lower alkoxy group which may be substituted by 1) a carboxyl group, 2) a hydroxyl group, 3) a cyano group, 4) a halogen atom, 5) an amino group which may be substituted by a lower alkyl group, 6) a pyridyl group, 7) a phenyl group, 8) a thienyl group, or 9) a lower alkoxy group,

e) a lower alkyl group which may be substituted by 1) an amino group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a (lower alkylamino)-lower alkyl group or a phenyl group, 2) a piperidinyl group which may be substituted by a lower alkylenedioxy group, 3) a morpholino group which may be substituted by a lower alkyl group, 4) a thiomorpholino group in which sulfur atom may be oxidized, 5) a piperazinyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a lower alkanoyl group or a phenyl-lower alkyl group, 6) pyrrolidinyl group which may be substituted by oxo group, or 7) an imidazolidinyl group which may be substituted by 1-3 groups selected from the group consisting of a lower alkyl group and oxo group,

f) an amino group which may be substituted by 1) a lower alkoxycarbonyl group, 2) a lower alkanesulfonyl group, 3) a carbamoyl group which may be substituted by a lower alkyl group a lower alkyl-phenyl group, 4) a lower alkanoyl group, 5) a lower alkyl group, 6) a lower alkenyl group, or 7) a thiocarbamoyl group which may be substituted by a lower alkyl group,

g) a carbamoyl group which may be substituted by 1) a lower alkyl group, 2) a hydroxy-lower alkyl group, 3) a morpholino-lower alkyl group, 4) a phenyl-lower alkyl group, or 5) a lower alkanesulfonyl group,

h) a sulfamoyl group which may be substituted by a lower alkyl group,

i) a lower alkenyloxy group,

j) a lower alkylenedioxy group,

k) a cyano group,

l) a lower alkylthio group, and
m) a lower alkanesulfonyl group.

20. The pharmaceutical composition according to claim 17 or 19, wherein R^1 is 1) hydrogen atom, 2) a halogen atom, 3) a lower alkanoylamino group, 4) a lower alkoxycarbonylamino group, 5) a lower alkanesulfonylamino group which may be substituted by a halogen atom, 6) a benzenesulfonylamino group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 7) thiophenesulfonylamino group, 8) an ureido group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, 9) a lower alkyl-thioureido group, or 10) a lower alkylsulfamoylamino group, R^2 is a halogen atom, R^3 is hydrogen atom or a halogen atom, and R^6 is a phenyl group which may have 1-3 substituents selected from the group consisting of 1) a lower alkoxy group, 2) a lower alkyl group which may be substituted by a group selected from the group consisting of a lower alkylamino group, a hydroxy-lower alkylamino group, a lower alkylamino-lower alkylamino group, piperidinyl group, a lower alkyl-piperidinyl group, morpholino group, a lower alkyl-morpholino group, a thiomorpholino group, piperazinyl group, a lower alkyl-piperazinyl group, a lower alkanoyl-piperazinyl group, and a pyrrolidinyl group, 3) a sulfamoyl group which may be substituted by a lower alkyl group, 4) a carbamoyl group which may be substituted by a lower alkyl group.

21. The pharmaceutical composition according to claim 20, wherein R^1 is hydrogen atom, R^3 is a halogen atom, and R^6 is 2-(lower alkoxy)phenyl group, 2,6-di(lower alkoxy)phenyl group, 2,6-di(lower alkoxy)-4-[[N,N-di(lower alkyl)amino]lower alkyl]phenyl group, 2,6-di(lower alkoxy)-

4-[(4-lower alkyl-1-piperazinyl)lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[1-piperidinyl-lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[N,N-di(lower alkyl)carbamoyl]phenyl group or 2,6-di(lower alkyl)-4-[(morpholino)lower alkyl]phenyl group.

22. The pharmaceutical composition according to claim 21, wherein a lower alkoxy group is methoxy group.

23. The pharmaceutical composition comprising a therapeutically effective amount of:

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(1-piperidinomethyl)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-methylpiperazinyl)amino]phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N,N-dimethylamino)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N,N-dimethylcarbamoyl)phenyl]-L-phenylalanine;

N-(2,6-dichloro-4-hydroxybenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2-ethoxy-6-methoxyphenyl)-L-phenylalanine;

N-(2,6-difluorobenzoyl)-4-(2-6,dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2,3-methylenedioxy-6-methoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethy)-4-(2,6-

dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2,4,6-trimethoxyphenyl)-L-phenylalanine;

N-[2,6-dichloro-4-[(trifluoromethanesulfonyl)amino]-benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine; or

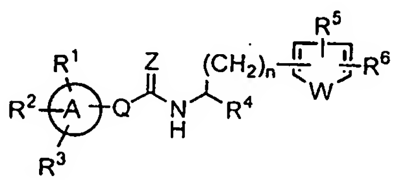
N-[2,6-dichloro-4-[(2-thienylsulfonyl)amino]benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

or a lower alkyl ester thereof;

or a pharmaceutically acceptable salt thereof;

and a pharmaceutically acceptable carrier or diluent.

24. A method for treating or preventing conditions caused by α_4 mediated cell adhesion in a patient which comprises administering to said patient an effective amount of a compound of the formula [I]:



[I]

wherein

Ring A is an aromatic hydrocarbon ring or a heterocyclic ring;

Q is a bond, a carbonyl group, a lower alkylene group which may be substituted by a hydroxyl group or phenyl group, a lower alkenylene group, or a -O-(lower alkylene)-group;

n is an integer of 0, 1 or 2;

W is oxygen atom, sulfur atom, a -CH=CH- group or a -N=CH- group;

Z is oxygen atom or sulfur atom;

R^1, R^2 and R^3 are the same or different and are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a substituted or unsubstituted lower alkyl group,

d) a substituted or unsubstituted lower alkoxy group,

e) a nitro group,

f) a substituted or unsubstituted amino group,

g) a carboxyl group or an amide or an ester thereof,

h) a cyano group,

i) a lower alkylthio group,

j) a lower alkanesulfonyl group,

k) a substituted or unsubstituted sulfamoyl group,

l) a substituted or unsubstituted aryl group,

m) a substituted or unsubstituted heterocyclic group, and

n) hydroxyl group;

or two of R^1, R^2 and R^3 may combine each other at the terminal thereof to form a lower alkylenedioxy group;

R^4 is tetrazolyl group, a carboxyl group, or an amide or an ester thereof;

R^5 is a group selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) a substituted or unsubstituted amino group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a substituted or unsubstituted lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom, and

i) 2-oxopyrrolidinyl group;

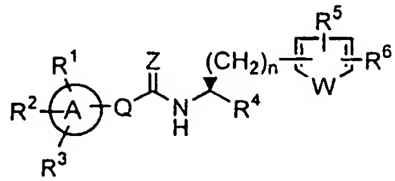
R^6 is a group selected from the group consisting of :

a) a substituted or unsubstituted phenyl group, and

b) a substituted or unsubstituted heteroaryl group;

or a pharmaceutically acceptable salt thereof.

25. The method according to claim 24, wherein the chemical structure is formula [I-A]:



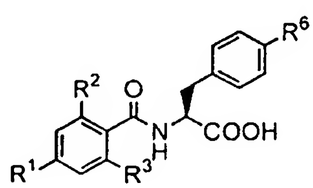
[I-A]

wherein symbols are the same as defined above.

26. The method according to claim 25, with the proviso that when Ring A is a benzene ring, the ring is not substituted with methyl group in the 3- and the 5-positions or in the 2- and the 4-positions;

27. The method according to claim 25, with the additional proviso that when Ring A is a benzene ring, the ring is substituted in at least one of 2- and 6-positions.

28. The method according to claim 25, wherein the chemical structure is formula [I-B]:



[I-B]

wherein symbols are the same as defined above.

29. The method according to claim 28, wherein

R^1 is hydrogen atom, a halogen atom, carboxyl group, carbamoyl group, nitro group, a substituted or unsubstituted amino group, a substituted or unsubstituted heterocyclic ring;

R^2 is hydrogen atom, a lower alkyl group or a halogen atom;

R^3 is hydrogen atom, a lower alkyl group or a halogen atom;

R^6 is a phenyl group which may be substituted at 2-, 4-, and/or 6-position of the phenyl group by a group selected from the group consisting of:

1) a halogen atom,

2) a substituted or unsubstituted lower alkoxy group,

3) a substituted or unsubstituted lower alkyl group ,

4) a substituted or unsubstituted amino group,

5) a substituted or unsubstituted carbamoyl group, and

6) a substituted or unsubstituted sulfamoyl group.

30. The method according to claim 24, wherein

Ring A is a benzene ring, a pyridine ring, a pyrazine ring, a furan ring, an isoxazole ring, a benzofuran ring, a thiophene ring, a pyrrole ring, or an indole ring;

R^1, R^2 and R^3 are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a lower alkyl group which may be substituted by a halogen atom or a (halogenobenzoyl)amino group,

d) a lower alkoxy group which may be substituted by a halogen atom,

e) a nitro group,

f) an amino group which may be substituted by 1-2 groups selected from the group consisting of 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a halogenobenzoyl group, 4) a lower alkoxycarbonyl group, 5) a lower alkanesulfonyl group which may be substituted by a halogen atom, 6) a benzenesulfonyl group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 7) thiophenesulfonyl group, 8) a carbamoyl group which may be

substituted by a lower alkyl group, a lower alkyl-phenyl group, 9) a thiocarbamoyl group which may be substituted by a lower alkyl group, phenyl group, a phenyl-lower alkyl group, 10) a thiazolinyl group, and 11) a sulfamoyl group which may be substituted by a lower alkyl group;

g) a carboxyl group,

h) a carbamoyl group which may be substituted by a lower alkanesulfonyl group,

i) a lower alkoxycarbonyl group,

j) a cyano group,

k) a lower alkylthio group,

l) a lower alkanesulfonyl group,

m) a sulfamoyl group,

n) a phenyl group,

o) a pyrrolidinyl group which may be substituted by oxo group,

p) a pyrrolyl group which may be substituted by a group selected from the group consisting of 1) a lower alkanoyl group which may be substituted by a halogen atom, 2) a halogen atom, 3) formyl group, and 4) a lower alkyl group which may be substituted by hydroxy group,

q) a thienyl group,

r) a isoxazolyl group which may be substituted by a lower alkyl group,

s) a thiazolyl group,

t) a pyrazolyl group,

u) a pyrazinyl group,

v) a pyridyl group, and

w) hydroxyl group;

R^4 is selected from the group consisting of:

a) carboxyl group,

b) a lower alkoxycarbonyl group which may be substituted by 1) pyridyl group or 2) an amino group which may be substituted by a lower alkyl group,

c) a lower cycloalkoxy carbonyl group,

d) a carbamoyl group which may be substituted by a hydroxy group or a lower alkanesulfonyl group, and

e) a tetrazolyl group;

R^5 is selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) an amino group which may be substituted by a lower alkanoyl group, a lower alkoxycarbonyl group or a lower alkanesulfonyl group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a lower alkyl group which may be substituted by 1) hydroxyl group, or 2) an imino group which is substituted by hydroxyl group or a lower alkoxy group,

g) a lower alkoxy group,

h) a halogen atom,

i) 2-oxopyrrolidinyl group;

R^6 is the group selected from the group consisting of:

a) a phenyl group which may have 1-5 substituents selected from the group consisting of:

1) a halogen atom,

2) a nitro group,

3) a formyl group,

4) a hydroxyl group,

5) a carboxyl group,

6) a lower alkoxy group which may be substituted by a group selected from the group consisting of i) a carboxyl group or an amide or an ester thereof, ii) hydroxyl group, iii) a cyano group, iv) a halogen atom, v) an amino group which may be substituted by a lower alkyl group, vi) a pyridyl group, vii) a thiazolyl group which may be substituted by a lower alkyl group, viii) an isoxazolyl group which may be

substituted by a lower alkyl group, ix) a piperidyl group which may be substituted by a lower alkyl group, x) a pyrrolidinyl group which may be substituted by a lower alkyl group, xi) a phenyl group which may be substituted by a halogen atom, xii) a furyl group, xiii) a thienyl group, and xiv) a lower alkoxy group

7) a lower alkyl group which may be substituted by a group selected from the group consisting of i) a halogen atom, ii) hydroxyl group, iii) carboxyl group or an amide or an ester thereof, iv) a lower alkoxy group, v) an amino group which may be substituted by 1-2 groups selected from the group consisting of a lower alkyl group, a hydroxy-lower alkyl group, a (lower alkylamino)-lower alkyl group, phenyl-lower alkyl group, a phenyl group, and a pyridyl group, vi) a piperidinyl group which may be substituted by a lower alkylenedioxy group, an oxo group or hydroxy group, vii) a morpholino group which may be substituted by a lower alkyl group, viii) thiomorpholino group which may be oxidized, ix) piperazinyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a lower alkanoyl group or a phenyl-lower alkyl group, x) pyrrolidinyl group which may be substituted by oxo group, and xi) an imidazolidinyl group which may be substituted by 1-3 groups selected from the group consisting of a lower alkyl group and oxo group,

8) a lower alkenyl group which may be substituted by carboxyl group or an amide or an ester thereof,

9) an amino group which may be substituted by a group selected from the group consisting of i) a phenyl group, ii) a lower alkoxycarbonyl group, iii) a lower alkanesulfonyl group, iv) a carbamoyl group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, v) a lower alkanoyl group,

vi) a lower alkyl group, vii) a lower alkenyl group, and viii) a thiocarbamoyl group which may be substituted by a lower alkyl group,

10) a carbamoyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a morpholino-lower alkyl group, a phenyl-lower alkyl group or a lower alkanesulfonyl group,

11) a sulfamoyl group which may be substituted by a group consisting of i) a lower alkyl group, ii) a benzoyl group, iii) a lower alkoxycarbonyl group, and iv) a lower alkanoyl group,

12) a lower alkenyloxy group.

13) a lower alkylenedioxy group,

14) a piperazinylcarbonyl group which may be substituted by a lower alkyl group,

15) a lower alkanoyl group,

16) cyano group,

17) a lower alkylthio group,

18) a lower alkanesulfonyl group,

19) a lower alkylsulfinyl group, and

20) a group of the formula: $-(CH_2)_q-O-$
wherein q is an integer of 2 or 3;

b) a pyridyl group which may be substituted by a lower alkyl group;

c) a thienyl group which may be substituted by a group selected from the group consisting of:

1) a halogen atom,

2) a lower alkyl group which may be substituted by hydroxyl group,

3) cyano group,

4) formyl group,

5) a lower alkoxy group, and

6) a lower alkanoyl group;

d) a benzofuranyl group;

e) a pyrimidinyl group which may be substituted by a lower alkoxy group;

f) an isoxazolyl group which may be substituted by a lower alkyl group, and

g) a pyrrolyl group which may be substituted by a lower alkoxycarbonyl group.

31. The method according to claim 30, wherein

Ring A is a benzene ring,

Q is a bond,

W is a -CH=CH- group,

R^1 is selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a lower alkyl group,

d) a lower alkoxy group,

e) nitro group,

f) an amino group which may be substituted by a group selected from the group consisting of 1) a lower alkyl group, 2) a lower alkanoyl group, 3) a lower alkoxycarbonyl group, 4) a lower alkanesulfonyl group which may be substituted by a halogen atom, 5) a benzenesulfonyl group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 6) thiophenesulfonyl group, 7) a carbamoyl group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, 8) a thiocarbamoyl group which may be substituted by a lower alkyl group, and 9) a sulfamoyl group which may be substituted by a lower alkyl group,

g) carboxyl group

h) a carbamoyl group which may be substituted by a lower alkanesulfonyl group,

i) a lower alkanesulfonyl group,

j) a sulfamoyl group,

k) phenyl group,

l) a pyrrolidinyl group which may be substituted by oxo group,

l) a pyrrolyl group which may be substituted by a lower alkyl group,

m) a thienyl group,

n) an isoxazolyl group which may be substituted by a lower alkyl group,

o) a thiazolyl group

p) a pyrazolyl group,

q) a pyrazinyl group,

r) a pyridyl group, and

s) hydroxyl group;

R^2 is hydrogen atom, or a halogen atom;

R^3 is hydrogen atom, or a halogen atom;

R^4 is a) a carboxyl group,

b) a lower alkoxycarbonyl group which may be substituted by a lower alkyl-amino group, or

c) a carbamoyl group which may be substituted by a lower alkanesulfonyl group;

R^5 is selected from the group consisting of:

a) hydrogen atom,

b) an amino group which may be substituted by a lower alkanoyl group, a lower alkoxycarbonyl group or a lower alkanesulfonyl group,

c) a lower alkanoyl group,

d) a lower alkyl group which may be substituted by 1) hydroxyl group, or 2) an imino group which is substituted by hydroxyl group or a lower alkoxy group,

g) a lower alkoxy group, and

h) a halogen atom;

R^6 is a phenyl group which may have 1-5 substituents selected from the group consisting of:

a) a halogen atom,

b) a formyl group,

c) a hydroxyl group,

d) a lower alkoxy group which may be substituted by 1) a carboxyl group, 2) a hydroxyl group, 3) a cyano group, 4) a halogen atom, 5) an amino group which may be substituted by a lower alkyl group, 6) a pyridyl group, 7) a phenyl group, 8) a thienyl group, or 9) a lower alkoxy group,

e) a lower alkyl group which may be substituted by 1) an amino group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a (lower alkylamino)-lower alkyl group or a phenyl group, 2) a piperidinyl group which may be substituted by a lower alkylenedioxy group, 3) a morpholino group which may be substituted by a lower alkyl group, 4) a thiomorpholino group in which sulfur atom may be oxidized, 5) a piperazinyl group which may be substituted by a lower alkyl group, a hydroxy-lower alkyl group, a lower alkanoyl group or a phenyl-lower alkyl group, 6) pyrrolidinyl group which may be substituted by oxo group, or 7) an imidazolidinyl group which may be substituted by 1-3 groups selected from the group consisting of lower alkyl group and oxo group,

f) an amino group which may be substituted by 1) a lower alkoxycarbonyl group, 2) a lower alkanesulfonyl group, 3) a carbamoyl group which may be substituted by a lower alkyl group a lower alkyl-phenyl group, 4) a lower alkanoyl group, 5) a lower alkyl group, 6) a lower alkenyl group, or 7) a thiocarbamoyl group which may be substituted by a lower alkyl group,

g) a carbamoyl group which may be substituted by 1) a lower alkyl group, 2) a hydroxy-lower alkyl group, 3) a

morpholino-lower alkyl group, 4) a phenyl-lower alkyl group, or 5) a lower alkanesulfonyl group,

h) a sulfamoyl group which may be substituted by a lower alkyl group,

i) a lower alkenyloxy group,

j) a lower alkylenedioxy group,

k) a cyano group,

l) a lower alkylthio group, and

m) a lower alkanesulfonyl group.

32. The method according to claim 29 or 31, wherein R^1 is 1) hydrogen atom, 2) a halogen atom, 3) a lower alkanoylamino group, 4) a lower alkoxycarbonylamino group, 5) a lower alkanesulfonylamino group which may be substituted by a halogen atom, 6) a benzenesulfonylamino group which may be substituted by a lower alkyl group, a trihalogeno-lower alkyl group, a halogen atom or a lower alkoxy group, 7) thiophenesulfonylamino group, 8) an ureido group which may be substituted by a lower alkyl group or a lower alkyl-phenyl group, 9) a lower alkyl-thioureido group, or 10) a lower alkylsulfamoylamino group, R^2 is a halogen atom, R^3 is hydrogen atom or a halogen atom, and R^6 is a phenyl group which may have 1-3 substituents selected from the group consisting of 1) a lower alkoxy group, 2) a lower alkyl group which may be substituted by a group selected from the group consisting of a lower alkylamino group, a hydroxy-lower alkylamino group, a lower alkylamino-lower alkylamino group, piperidinyl group, a lower alkyl-piperidinyl group, morpholino group, a lower alkyl-morpholino group, a thiomorpholino group, piperazinyl group, a lower alkyl-piperazinyl group, a lower alkanoyl-piperazinyl group, and a pyrrolidinyl group, 3) a sulfamoyl group which may be substituted by a lower alkyl group, 4) a carbamoyl group which may be substituted by a lower alkyl group.

33. The method according to claim 32, wherein R^1 is hydrogen atom, R^3 is a halogen atom, and R^6 is 2-(lower alkoxy)phenyl group, 2,6-di(lower alkoxy)phenyl group, 2,6-di(lower alkoxy)-4-[[N,N-di(lower alkylamino)lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[(4-lower alkyl-1-piperazinyl)lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[1-piperidinyl-lower alkyl]phenyl group, 2,6-di(lower alkoxy)-4-[N,N-di(lower alkyl)carbamoyl]phenyl group or 2,6-di(lower alkoxy)-4-[(morpholino)lower alkyl]phenyl group.

34. The method according to claim 33, wherein a lower alkoxy group is methoxy group.

35. A method for treating or preventing conditions caused by α_4 mediated cell adhesion in a patient which comprises administering to said patient an effective amount of :

N-(2,6-dichlorobenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(piperidinomethyl)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-[(4-methylpiperazinyl)amino]phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(morpholinomethyl)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N,N-dimethylamino)phenyl]-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-[2,6-dimethoxy-4-(N,N-dimethylcarbamoyl)phenyl]-L-phenylalanine;

N-(2,6-dichloro-4-hydroxybenzoyl)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2-ethoxy-6-methoxyphenyl)-

L-phenylalanine;

N-(2,6-difluorobenzoyl)-4-(2-6,dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2,3-methylenedioxy-6-methoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-3-(1-hydroxyethy)-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

N-(2,6-dichlorobenzoyl)-4-(2,4,6-trimethoxyphenyl)-L-phenylalanine;

N-[2,6-dichloro-4-[(trifluoromethanesulfonyl)amino]-benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine; or

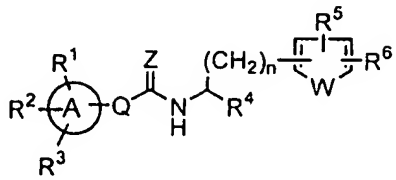
N-[2,6-dichloro-4-[(2-thienylsulfonyl)amino]benzoyl]-4-(2,6-dimethoxyphenyl)-L-phenylalanine;

or a lower ester thereof;
or pharmaceutically acceptable salt thereof.

36. The method according to one of claims 24-35, wherein said condition is selected from the group consisting of rheumatoid arthritis, asthma, psoriasis, eczema, contact dermatitis and other skin inflammatory diseases, diabetes, multiple sclerosis, systemic lupus erythematosus (SLE), inflammatory bowel disease including ulcerative colitis and Crohn's disease, and other diseases involving leukocyte infiltration of the gastrointestinal tract, or other epithelial lined tissues, such as skin, urinary tract, respiratory airway, and joint synovium.

37. The method according to claim 36, wherein said condition is inflammatory bowel disease including ulcerative colitis and Crohn's disease.

38. A process for preparing the compound of the formula [I]:



[I]

wherein

Ring A is an aromatic hydrocarbon ring or a heterocyclic ring;

Q is a bond, a carbonyl group, a lower alkylene group which may be substituted by a hydroxyl group or phenyl group, a lower alkenylene group, or a -O-(lower alkylene)-group;

n is an integer of 0, 1 or 2;

W is oxygen atom, sulfur atom, a -CH=CH- group or a -N=CH- group;

Z is oxygen atom or sulfur atom;

R^1, R^2 and R^3 are the same or different and are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a substituted or unsubstituted lower alkyl group,

d) a substituted or unsubstituted lower alkoxy group,

e) a nitro group,

f) a substituted or unsubstituted amino group,

g) a carboxyl group or an amide or an ester thereof,

h) a cyano group,

i) a lower alkylthio group,

j) a lower alkanesulfonyl group,

k) a substituted or unsubstituted sulfamoyl group,

l) a substituted or unsubstituted aryl group,

m) a substituted or unsubstituted heterocyclic group, and

n) hydroxyl group;

or two of R^1, R^2 and R^3 may combine each other at the terminal thereof to form a lower alkylenedioxy group;

R^4 is tetrazolyl group, a carboxyl group, or an amide or an ester thereof;

R^5 is a group selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) a substituted or unsubstituted amino group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a substituted or unsubstituted lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom,

i) 2-oxopyrrolidinyl group;

R^6 is a group selected from the group consisting of :

a) a substituted or unsubstituted phenyl group, and

b) a substituted or unsubstituted heteroaryl group;

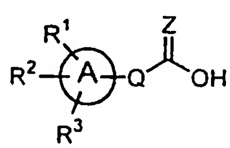
with the proviso that

when Ring A is a benzene ring, the ring is not substituted with a methyl group in the 3- and the 5-positions or in the 2- and the 4- positions;

or a pharmaceutically acceptable salt thereof,

comprising:

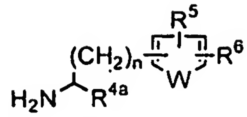
(1) condensing a compound of the formula [II]:



[II]

wherein the symbols are the same as defined above,

a salt thereof or a reactive derivative thereof with a compound of the formula [III]:

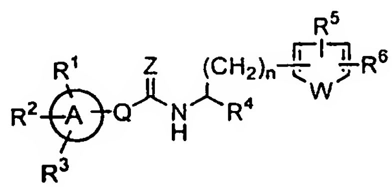

[III]

wherein R^{4a} is an ester group, and other symbols are the same as defined above, or a salt thereof,

(2) converting the ester group into a carboxyl group, if desired, and

(3) converting the carboxyl group of the resulting compound into an ester group, an amide group, a tetrazolyl group or a pharmaceutically acceptable salt thereof, if further desired.

39. A process for preparing the compound of the formula [I]:


[I]

wherein

Ring A is an aromatic hydrocarbon ring or a heterocyclic ring;

Q is a bond, a carbonyl group, a lower alkylene group which may be substituted by a hydroxyl group or phenyl group, a lower alkenylene group, or a -O-(lower alkylene)- group;

n is an integer of 0, 1 or 2;

W is oxygen atom, sulfur atom, a -CH=CH- group or a -N=CH- group;

Z is oxygen atom or sulfur atom;

R^1, R^2 and R^3 are the same or different and are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a substituted or unsubstituted lower alkyl group,

d) a substituted or unsubstituted lower alkoxy group,

e) a nitro group,

f) a substituted or unsubstituted amino group,

g) a carboxyl group or an amide or an ester thereof,

h) a cyano group,

i) a lower alkylthio group,

j) a lower alkanesulfonyl group,

k) a substituted or unsubstituted sulfamoyl group,

l) a substituted or unsubstituted aryl group,

m) a substituted or unsubstituted heterocyclic group, and

n) hydroxyl group,

or two of R^1, R^2 and R^3 may combine each other at the terminal thereof to form a lower alkylenedioxy group;

R^4 is tetrazolyl group, a carboxyl group, or an amide or an ester thereof;

R^5 is a group selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) a substituted or unsubstituted amino group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a substituted or unsubstituted lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom, and

i) 2-oxopyrrolidinyl group;

R^6 is a group selected from the group consisting of :

a) a substituted or unsubstituted phenyl group, and

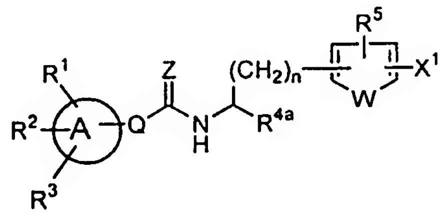
b) a substituted or unsubstituted heteroaryl group;

with the proviso that

when Ring A is a benzene ring, the ring is not substituted with a methyl group in the 3- and the 5-positions or in the 2- and the 4- positions;

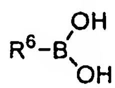
or a pharmaceutically acceptable salt thereof, comprising:

(1) reacting a compound of the formula [IV]:



[IV]

wherein X^1 is a leaving group, R^{4a} is an ester group, and other symbols are the same as defined above,
with a compound of the formula [V]:



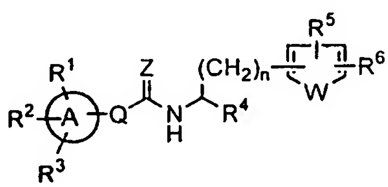
[V]

wherein the symbols are the same as defined above,

(2) converting the ester group into a carboxyl group, if desired, and

(3) converting the carboxyl group of the resulting compound into an ester group, an amide group or a pharmaceutically acceptable salt thereof, if further desired.

40. A process for preparing the compound of the formula [I]



[I]

wherein

Ring A is an aromatic hydrocarbon ring or a heterocyclic ring;

Q is a bond, a carbonyl group, a lower alkylene group which may be substituted by a hydroxyl group or phenyl

group, a lower alkenylene group, or a -O-(lower alkylene)-group;

n is an integer of 0, 1 or 2;

W is oxygen atom, sulfur atom, a -CH=CH- group or a -N=CH- group;

Z is oxygen atom or sulfur atom;

R^1, R^2 and R^3 are the same or different and are selected from the group consisting of:

a) hydrogen atom,

b) a halogen atom,

c) a substituted or unsubstituted lower alkyl group,

d) a substituted or unsubstituted lower alkoxy group,

e) a nitro group,

f) a substituted or unsubstituted amino group,

g) a carboxyl group or an amide or an ester thereof,

h) a cyano group,

i) a lower alkylthio group,

j) a lower alkanesulfonyl group,

k) a substituted or unsubstituted sulfamoyl group,

l) a substituted or unsubstituted aryl group,

m) a substituted or unsubstituted heterocyclic group, and

n) hydroxyl group;

or two of R^1, R^2 and R^3 may combine each other at the terminal thereof to form a lower alkylenedioxy group;

R^4 is tetrazolyl group, a carboxyl group, or an amide or an ester thereof;

R^5 is a group selected from the group consisting of:

a) a hydrogen atom,

b) a nitro group,

c) a substituted or unsubstituted amino group,

d) a hydroxyl group,

e) a lower alkanoyl group,

f) a substituted or unsubstituted lower alkyl group,

g) a lower alkoxy group,

h) a halogen atom, and

i) 2-oxopyrrolidinyl group;

R^6 is a group selected from the group consisting of :

a) a substituted or unsubstituted phenyl group, and

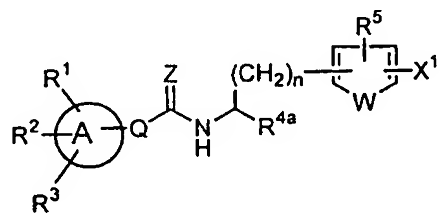
b) a substituted or unsubstituted heteroaryl group;

with the proviso that

when Ring A is a benzene ring, the ring is not substituted with a methyl group in the 3- and the 5-positions or in the 2- and the 4- positions;

or a pharmaceutically acceptable salt thereof, comprising:

(1) converting a compound of the formula [IV]:



[IV]

wherein X^1 is a leaving group, R^{4a} is an ester group, and other symbols are the same as defined above, to the corresponding organotin compound,

(2) reacting the organotin compound with a compound of the formula [VIII]:

R^6-X [VIII]

wherein X is a leaving group and R^6 is the same as defined above,

(3) converting the ester group of the compound of the formula [Ia] into a carboxyl group, if desired, and

(4) converting the carboxyl group of the resulting compound into an ester group, an amide group or a pharmaceutically acceptable salt thereof, if further desired.

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/US 99/00993

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C233/87 C07C237/30 C07C271/28 C07C311/09 C07D295/14
C07D333/34 A61K31/245 A61K31/33

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
E	WO 99 10312 A (F. HOFFMANN-LA ROCHE) 4 March 1999 see page 15 - page 16; examples 72-84,97-102 see claims; example 170 ---	1-4, 12-15
X	CHEMICAL ABSTRACTS, vol. 65, no. 10, 7 November 1966 Columbus, Ohio, US; abstract no. 15302d, S. V. SOKOLOV ET AL.: "Derivaives of 1-phenyl-2,5-bis(chlormethyl)pyrrolidine" column 2; XP002101493 see abstract & ZH. ORGAN. KHIM., vol. 2, no. 6, 1966, pages 1088-1092, --- -/--	1,2

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 1999	17/05/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zervas, B

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	WO 96 22966 A (BIOGEN) 1 August 1996 see page 23 - page 36; claims -----	1-39

1

International application No.

PCT/US 99/00993

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 24-37
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 24-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern   ıal Application No
PCT/US 99/00993

Patent document cited in search report		Publication date	Patent family member(s)			Publication date
WO 9910312	A	04-03-1999	NONE			
WO 9622966	A	01-08-1996	AU	4911596	A	14-08-1996
			BG	101841	A	30-04-1998
			BR	9606778	A	06-01-1998
			CA	2211181	A	01-08-1996
			CN	1177343	A	25-03-1998
			CZ	9702340	A	18-03-1998
			EP	0805796	A	12-11-1997
			FI	973087	A	22-09-1997
			HU	9702461	A	28-04-1998
			JP	10513160	T	15-12-1998
			NO	973384	A	19-09-1997
			PL	321848	A	22-12-1997
			SK	98797	A	04-02-1998